UNIVERSITY OF CALIFORNIA,
IRVINE

Assigning the Absolute Configuration of Sulfoxides and Cyclic Secondary Amines using the Competing Enantioselective Conversion (CEC) Method

DISSERTATION

Submitted in satisfaction of the requirements
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In Chemistry

by

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Dissertation Committee:
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LIST OF ABBREVIATIONS

BINOL	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
DCC	*N,N'*-dicyclohexylcarbodiimide
DMF	*N,N'*-dimethylformamide
HFIP	hexafluoroisopropanol
HOBt	hydroxybenzotriazole
H_2O_2	hydrogen peroxide
$MesSO_2Cl$	2,4,6-trimethylbenzenesulfonyl chloride
MS	mass spectrometry
$NaBH_4$	sodium borohydride
$NaIO_4$	sodium metaperiodate
NMR	nuclear magnetic resonance
$RuCl_3$	ruthenium (III) trichloride
$SOCl_2$	thionyl chloride
TFA	trifluoroacetic acid
$Ti(OiPr)_4$	titanium tetraisopropoxide
$VO(acac)_2$	vanadyl acetylacetonate

CURRICULUM VITAE

EDUCATION

August 2016 to September 2019 (Anticipated)	University of California, Irvine (Irvine, CA) M. Sc. Organic Chemistry *Advisor: Scott D. Rychnovsky*
August 2011 to May 2015	University of Florida (Gainesville, FL) B.S., Chemistry (Emphasis in Biochemistry) *Advisors: Robert Huigens and Stephen Miller*

EXPERIENCE

University of California, Irvine **Irvine, CA**
Graduate Research Assistant Aug 2016 – Present
Advisor: Scott D. Rychnovsky

Determining the Absolute Configuration of Sulfoxides Using the Competing Enantioselective Conversion (CEC) Method

- Designing and developing a simple and effective method to assign the absolute configuration of sulfoxides using an oxidative approach. The method was being optimized to be analyzed by ^{1}H NMR.

Determining the Absolute Configuration of Heterocyclic Amines Using the Competing Enantioselective Conversion (CEC) Method

- Designing and developing a simple and effective method to assign the absolute configuration of heterocyclic amines using pseudo-enantiomeric acyl transfer reagents. The method is being optimized to be analyzed by tandem quadrupole mass spectrometry (TQ-MS), which permits the use of micrograms of material and requires no work-up or purification.

University of California, Irvine **Irvine, CA**
Teaching Assistant Aug 2016 – Present
General and Organic Chemistry Lectures and Labs

- Assist students with proper laboratory techniques such as chromatography, volumetric analysis, and calorimetry.
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Kraton Chemical Science and Technology Center **Savannah, GA**
Intern Jan 2016 – May 2016
Mentor: Jeff Warmkessel

- Led an aging study analyzing the effectiveness of the addition of various sterically hindered phenol, phosphite ester, amine-light stabilizer antioxidants added to resin polymer products which led to optimization and extension of commercial resin stability (shelf-life) from two weeks to several months.
- Collaboration with the analytical department on HPLC method development and validation to determine the degree of oxidation in polymer blends over time.
- Synthesis of Ziegler-type catalysts for use in the hydrogenation of polymer products

University of Florida **Gainesville, FL**
Undergraduate Research Associate May 2015 – December 2015
Advisor: Stephen Miller

- Extraction of various phytochemicals for use in the synthesis of commercial polyester thermoplastics. Organocatalyst synthesis for the production of biorenewable polymers.

University of Florida **Gainesville, FL**
Undergraduate Research Associate August 2014 – December 2015
Advisor: Robert Huigens

- Synthesis of tetracycline and fluoroisoquinoline derivatives and conduction of biological assays to determine the efficiency of biofilm inhibition.

SKILLS

- Thorough understanding of synthetic organic lab techniques, which include air-free reactions, handling pyrophoric reagents, normal and reverse-phase chromatography
- Understanding of instrumental protocol necessary for operation of High Performance Liquid Chromatography (HPLC), Mass-Spectrometry (MS), and Liquid Chromatography-Mass Spectrometry (LCMS), Gas Chromatography-Mass Spectrometry (GC-MS)
- Experienced in acquisition and interpretation of 1-D and 2-D nuclear magnetic resonance (NMR) experiments.
- Experience with curable resin technology and polymer blends
- Proficiency with Microsoft Office

To those who propped me up,

thank you for being there when times were tough

Chapter 1. Assigning the Absolute Configuration of Sulfoxides Using the Competing Enantioselective Conversion (CEC) Method

1.1 Abstract

Various metal-ligand catalyst systems were screened in order to determine if enantioselective oxidations were suitable as potential transformations for Competing Enantioselective Conversion (CEC) analysis. Optimization of CEC conditions allowed for analysis in the common solvent $CDCl_3$, which minimized analysis time by avoiding a workup step. Increasing the equivalents of oxidant from 1 to 5 afforded greater difference in selectivity over a 16.5 hour time frame of the analysis, which allows for more accurate determination of absolute configuration. Synthesis of enantioenriched sulfoxides for substrate testing began using the Senanayake protocol. Initial CEC results indicated a lack of selectivity or a mismatch in selectivity that prompted the investigation of the Uemura system. The Uemura system was unreliable in our hands, and the project was ultimately abandoned.

1.2 Introduction

1.2.1 Importance of Three-Dimensional Configuration

The three-dimensional molecular structures of organic compounds are essential to the chemical reactivity and biological activity of synthetic molecules and natural products. As such, methods that enable determining the absolute configuration of organic molecules are of great interest to chemists in academic and industrial settings. Current methods to assign absolute stereochemistry include vibrational circular dichroism (VCD), Mosher's method, and X-ray crystallographic analysis.[1]

VCD analysis works through a two-part sequence involving experimentally subjecting a chiral molecule to left and right circularly polarized infrared light, and computationally generating a circular dichroism spectrum for each enantiomer of a target compound.[2] The experimentally derived spectra are then compared to the computational models; if one of the computational spectra for an enantiomer match the experimentally generated spectra the absolute configuration of the compound can be assigned. Mosher's method involves reacting both enantiomers of a chiral derivatizing agent, α-methoxy-α-trifluoromethylphenyl acetic acid (MTPA) with a single enantiomer of an enantiopure alcohol or amine in two separate reaction vessels.[3] The resulting diastereomeric ester or amide produced are then purified by chromatography and analyzed via ^{1}H or ^{19}F NMR spectroscopy. Using an established mnemonic, the absolute configuration may be established by comparing the change in chemical shifts of the protons near the chiral center of interest. X-ray crystallography may also be used to assign the absolute configuration of crystalline compounds through an analysis of a molecule's diffraction pattern.[4]

While the methods described previously are well-established and routinely used to assign the absolute configuration of chiral compounds, each has limitations. VCD requires significant

computational power to generate the theoretical spectra, and experimental spectra often contain instrument or solvent artifacts that complicate analysis. While Mosher's method is commonly performed, it requires a substantial amount of material and requires approximately two days' worth of routine lab work and NMR spectroscopy analysis to complete the assignment of absolute configuration. X-ray crystallography is considered to be the most accurate, but many small molecules are not crystalline, and the time needed to grow crystals of the proper size, quality, and shape required for analysis can range anywhere from days to weeks. Unfortunately, even with the methods available today, many compounds have been misassigned.[5] Therefore, there is a need for the development of a practical, robust, and rapid method for the assignment of absolute stereochemistry of enantioenriched stereocenters.

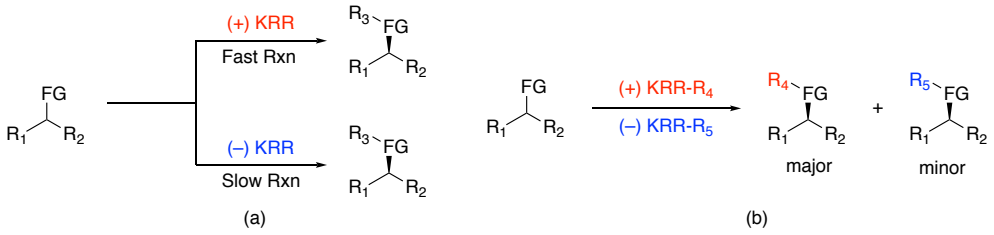


Figure 3-1. Generic examples of the two approaches used in the CEC method to assign absolute configuration of enantiopure substrates. FG = functional group. KRR = kinetic resolution reagent.

1.2.2 Introduction to CEC Method

Over the past several years, the Rychnovsky group has been developing the Competing Enantioselective Conversion (CEC) method to determine the absolute configuration of various enantioenriched functional groups. The initial CEC method (Figure 1-1, a), involves running two parallel reactions with the same enantioenriched substrate and each of the two enantiomers of a kinetic resolution reagent (KRR). The substrate preferentially reacts with one enantiomer of the KRR, which is reflected by differences in conversion rates after ^{1}H NMR spectroscopic analysis. Using an empirically derived mnemonic, the absolute configuration of the substrate can be

extrapolated based on which KRR reacted faster with the substrate. Using this strategy, successful CEC methods were developed for secondary alcohols, lactams, and oxazolidinones.[6-8]

While these initial applications were successful and avoided the need for chromatography, they still required running two separate reactions and involved spectroscopic analysis to determine absolute configuration. We sought to improve the method further by implementing a mass spectrometry analysis that would enable us to perform the test with a single reaction and a quick, user friendly analysis. This goal was realized in our group's second generation approach of the CEC method (Figure 1-1, b), which uses one flask with two competing pseudoenantiomeric KRR's (pKRRs) present in excess while still relying on the relative rate of reaction between the two reagents and the substrate. The reaction produces pseudoenantiomeric products, and the ratio of these products can be analyzed via mass spectrometry to identify the fast-reacting, "matched" enantiomer. This approach has been implemented in the assignment of absolute stereochemistry for primary amines and cyclic secondary amines.[9-10] With a wide array of asymmetric transformations at the disposal of the synthetic chemist, we also sought to expand the scope of our CEC method, to analyze different types of substrates.

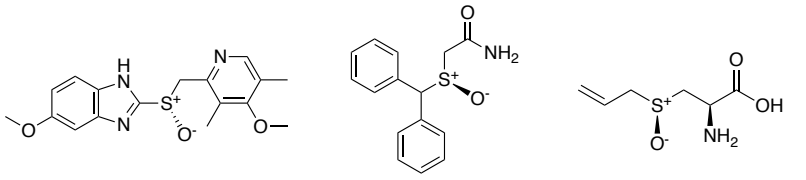


Figure 1-2. Examples of enantioenriched sulfoxide-containing therapeutics and natural products.

The most current application of the CEC method being developed in the Rychnovsky lab involves the application of enantioselective oxidation reactions. Enantioselective oxidations represent some of the first effective enantioselective methods, and among the many approaches

reported, metal-catalyzed enantioselective oxidations appear to be the most versatile in terms of the profile of catalytic systems available to perform oxidative transformations. [11] Specifically, we chose to focus on the sulfoxide functionality for a variety of reasons. Enantioenriched sulfoxides are versatile building blocks present in some natural products such as alliin, a chemical component responsible for the taste of garlic, as well as chiral auxiliaries in organic synthesis.[12-13] They have also been synthesized and studied for their bioactivity, and several trademarked pharmaceuticals such as armodafinil and esomeprazole contain chiral sulfoxides (Figure 1-2). In addition, a plethora of methods have been disclosed that provide access to chiral sulfoxides through asymmetric oxidations, reductions, and kinetic resolutions. This suggested that we would be able to readily synthesize a broad library of chiral sulfoxides, and if necessary, explore a variety of catalytic systems to optimize our desired CEC oxidation method. Given the prevalence of chiral sulfoxides, the development of a reliable CEC method to determine the absolute configuration of these compounds could prove to be useful in both academic and industrial settings.

1.3 Results and Discussion

1.3.1 Development of Oxidative CEC Method using Sun Catalyst System

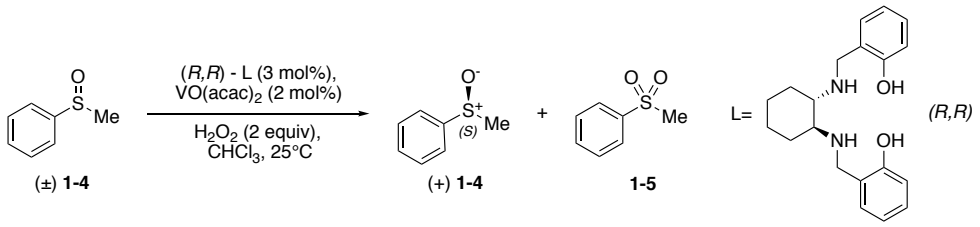
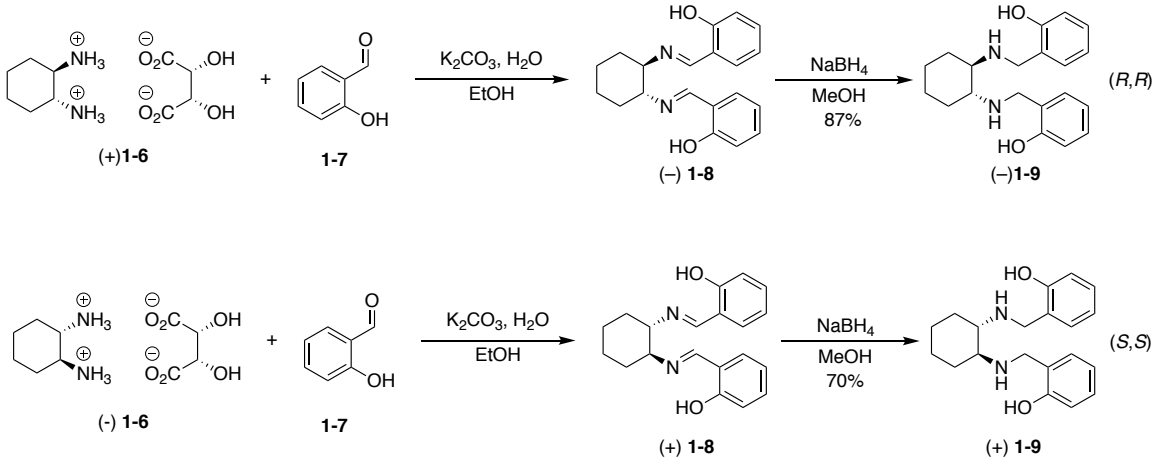


Figure 1-3. Kinetic resolution of sulfoxides catalyzed by Sun's vanadium-salen system

After searching the literature for suitable catalyst systems, the work of Sun was selected as the initial starting point for this project due to the ease of synthesis of the ligands as well as the commercial availability of $VO(acac)_2$ (Figure 1-3).[14] Synthesis of the salen ligands began with condensation with respective chiral enantiomers of commercially available cyclohexanediamines

(+) **1-6** and (–) **1-6** onto salicylic acid (**1-7**) to afford Schiff bases (+) **1-8** and (–) **1-8** respectively. Subsequent reduction with $NaBH_4$ and recrystallization from hexanes afforded enantiopure salen ligands (–) **1-9** and (+) **1-9**, respectively (Scheme 1-1), in accordance with the published procedure.[14]



Scheme 1-1. Synthetic approach towards chiral salen ligands

In order to verify the reported selectivity and enantioselectivity, racemic methyl phenyl sulfoxide (±) **1-4** was chosen as a model substrate for kinetic resolution using $VO(acac)_2$ and either chiral ligand (–) **1-9** or (+) **1-9**. After several failed attempts at replicating previously reported results, the literature was further consulted to find evidence of application of this catalyst system in asymmetric oxidations of sulfides. Unfortunately, it was discovered that two separate groups were unable to replicate the results of Sun. [15,16]

1.3.2 Redevelopment of Oxidative CEC Method using Gao and Uemura systems

After the failure of the Sun oxidation, we turned our attention towards two other catalytic system developed by Gao[17] and Uemura (Figure 1-4).[18] The Uemura method was chosen because it uses inexpensive and commercially available BINOL ligands (–) **1-12** or (+) **1-12,** in conjunction with $Ti(OiPr)_4$. While the Gao method would require the synthesis of chiral ligands, it was pursued because of its wide substrate scope.

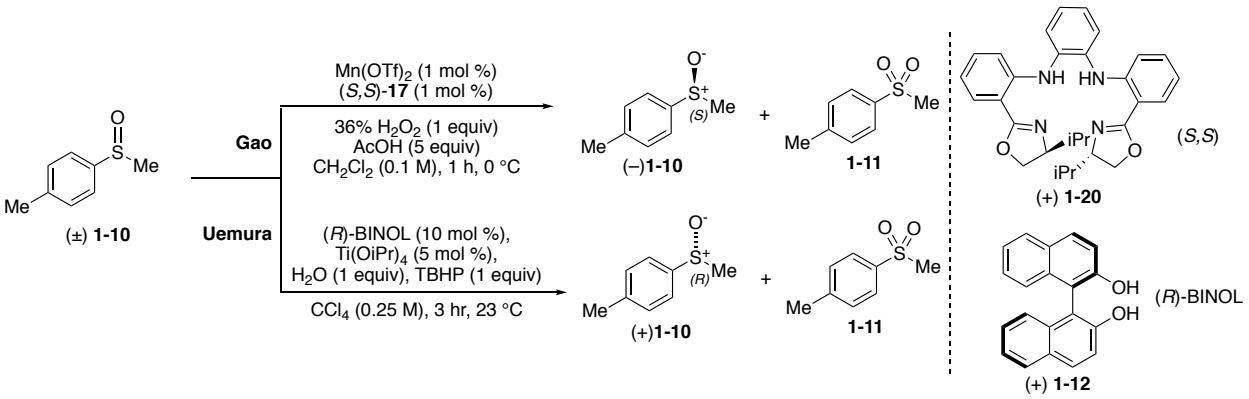
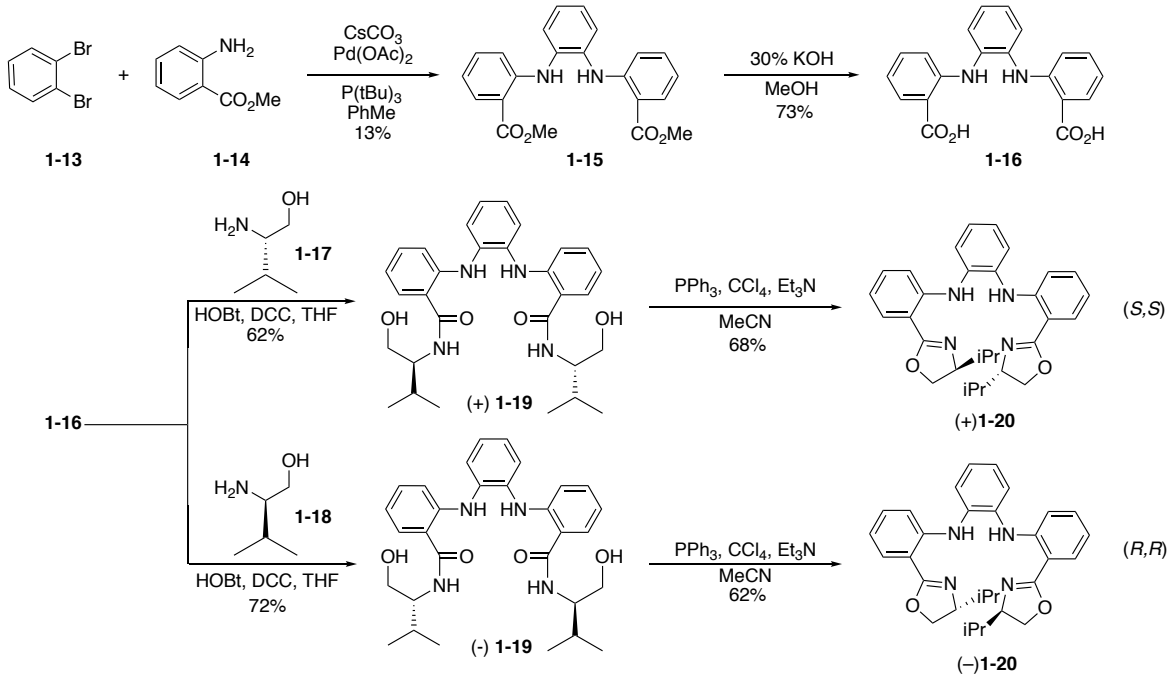


Figure 1-4. Kinetic resolution of sulfoxides catalyzed by the Gao and Uemura catalyst sytems

Synthesis of porphyrin-inspired Gao ligands (–) **1-20** or (+) **1-20** proceeded with Buchwald-Hartwig coupling of 1,2-dibromobenzene (**1-13**) and methyl anthranilate (**1-14**) to afford bis-coupled amine **1-15** (Scheme 1-2). Hydrolysis of both esters afforded carboxylic acid **1-16**, which then underwent DCC/HOBt mediated amide coupling with either L- or D-Valinol (**1-17, 1-18**) to afford chiral amino alcohols (–) **1-19** and (+) **1-19** . Lastly, an Appel reaction and subsequent cyclization affords oxazoles (–) **1-20** and (+) **1-20**. [17]

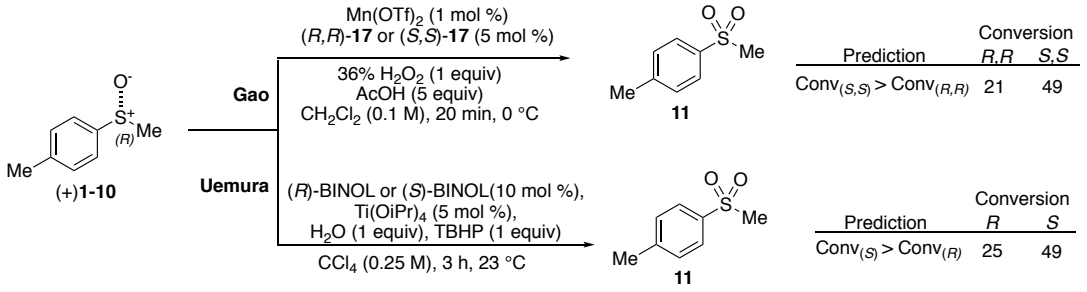


Scheme 1-2. Synthetic scheme towards porphyrin-inspired ligand.

With the ligands at hand, initial attempts at CEC reactions using (+) **1-10** as a test substrate were conducted to develop an empirical mnemonic for our method (Scheme 1-3). Based on the kinetic resolution data from the Gao catalyst systems, resolving of a racemic mixture of **10** would lead to enantiopure (–) **1-10.** From this result, we predicted that subjecting enantiopure (+) **1-10** to CEC conditions utilizing the Gao catalyst system would demonstrate selectivity such that the conversion to sulfone **1-11** would be faster for the (*S,S*) enantiomer of the ligand.

For the Uemura catalyst system, resolving of a racemic mixture of **10** would lead to enantiopure (+) **1-10**. Based on this data, we predicted that subjecting enantiopure (+) **1-10** to CEC conditions with this system would demonstrate selectivity such that the conversion to sulfone **1-11** would be faster for (*S*)-BINOL.

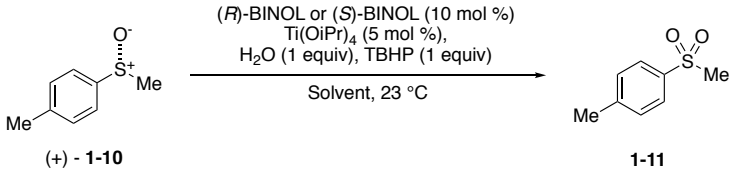
To our delight, the observed selectivity for both systems matched our predicted ones, concluding that both systems can be used for CEC analysis. Due to the commercial availability and inexpensiveness of both BINOL and $Ti(OiPr)_4$, we chose to continue further CEC studies using the Uemura catalyst system. With the catalyst system chosen and initial data point obtained, we can formulate our initial mnemonic. If there is an aryl group on the left and an alkyl substituent on the right of the sulfur atom of the sulfoxide and (*S*)-BINOL has faster conversion, we can conclude the sulfoxide oxygen is pointed backward with respect to the symmetry plane.



Scheme 1-3. Example of CEC conditions utilizing the Gao and Uemura systems along with predicted and observed outcomes of conversion rates

1.3.3 Optimization of CEC conditions using Uemura system

Optimization of CEC conditions proceeded with a deuterated solvent screen to determine if CEC analysis can be carried out in deuterated solvent, negating the need to quench and work up the experiment. Our solvent also needed to provide minimal overlap with the methyl peak adjacent to the sulfur atom. (Table 1-1). During solvent screening, the opposite enantiomer of our test substrate, (–) **1-10** was subjected to CEC conditions (Table 1-1, Entry 2) in order to determine if our system would display equal and opposite selectivity, given the change in absolute stereochemistry of our sulfur center. As expected, the BINOL/$Ti(OiPr)_4$ system was able to recognize the opposite enantiomer and displayed opposite selectivity. After screening, it was found that deuterated chloroform, $CDCl_3$, gave the greatest difference in selectivity while also minimizing overlap with the selected methyl peak and therefore was chosen as the solvent to continue further optimization.



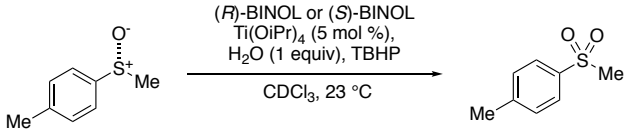
(+) - **1-10** **1-11**

Entry	Solvent	Time (h)	Conversion *R*	Conversion *S*
1	$CDCl_3$	3	20	59
2[a]	$CDCl_3$	3	50	24
3	CD_3OD	3	3	8
4	PhMe-d_6	3	56	68

Table 1-1. Deuterated solvent screen for Oxidative CEC ([a] (–) **1-10** used as test substrate)

Our next endeavor was to alter reaction concentration in relation to the substrate to reduce the amount of reagent material needed to conduct the experiments while still obtaining reliable results (Table 1-2). The concentration could be diluted five-fold from the initial concentration of 0.25 M with good selectivity. Further optimization was conducted at 0.1 M to minimize the time

required for the reactions to be completed. A study varying the equivalents of *tert*-butyl hydrogen peroxide (TBHP) was performed in order to achieve saturation reaction kinetics, such that the rate of the parallel reactions was independent of the reformation of the active catalyst system. Increasing equivalents of TBHP from 1 to 5 afforded greater difference in selectivity over a given time period, while addition of 10 equivalents showed little to no change in selectivity, suggesting that 5 equivalents was enough to saturate our catalytic system. Decreasing the amount of BINOL used in the reactions detrimentally decreases reaction conversion, while adding increased equivalents of BINOL showed no greater difference in selectivity. With this data in hand, the reaction conditions for CEC were considered optimized, and we turned our attention towards exploring the scope of the oxidation.



(+) - **1-10** **1-11**

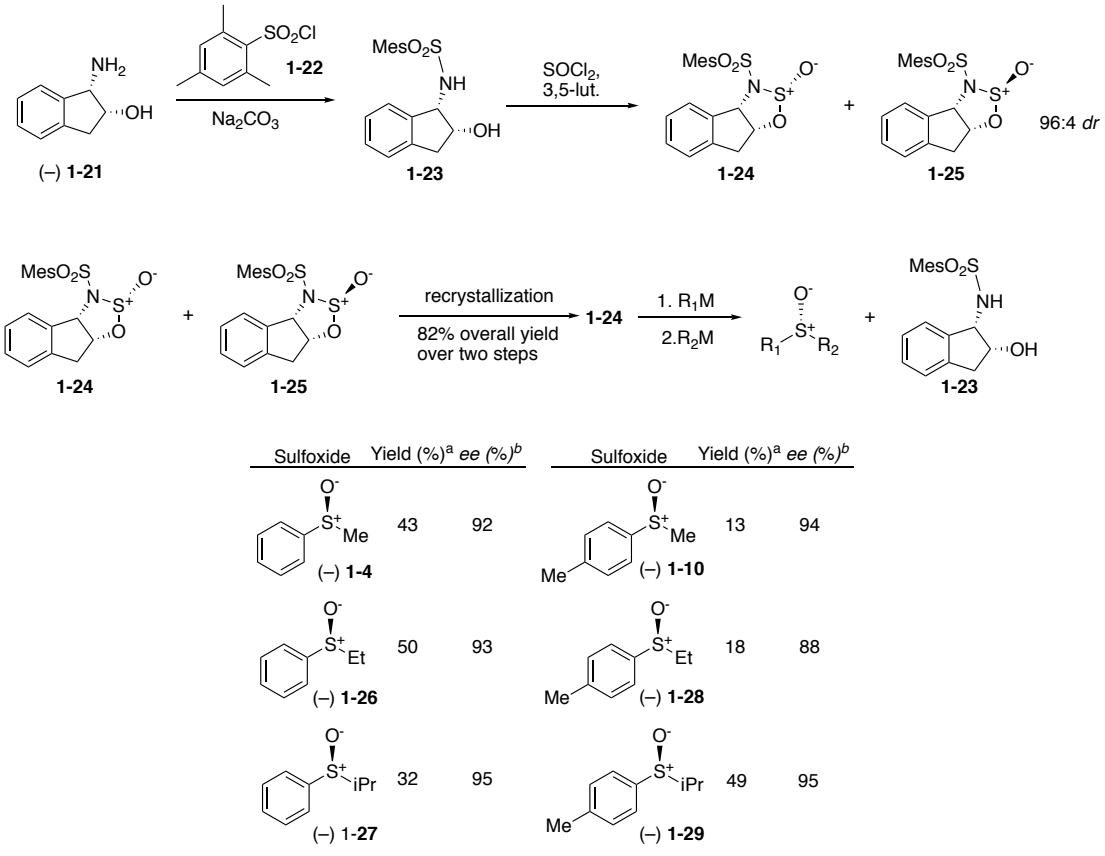
Entry	Conc. (M)	mol% BINOL	mol% $Ti(OiPr)_4$	equiv TBHP	Time (h)	Conversion *R*	Conversion *S*
1	0.1	10	5	1	16.5	35	61
2	0.1	10	5	3	16.5	38	80
3	0.1	10	5	5	16.5	44	98
4	0.1	10	5	10	16.5	47	96
5	0.05	5	5	5	20	8	11
6	0.05	10	5	5	20	22	50
7	0.05	25	5	5	20	24	54

Table 1-2. Complete optimization of Oxidative CEC conditions[a] ([a] experiments conducted in $CDCl_3$)

1.3.4 Enantioenriched Sulfoxide Synthesis

In order to explore the scope, we first had to synthesize a variety of enantiopure sulfoxides. We chose to employ the Senanayake protocol, where commercially available chiral amino indanol

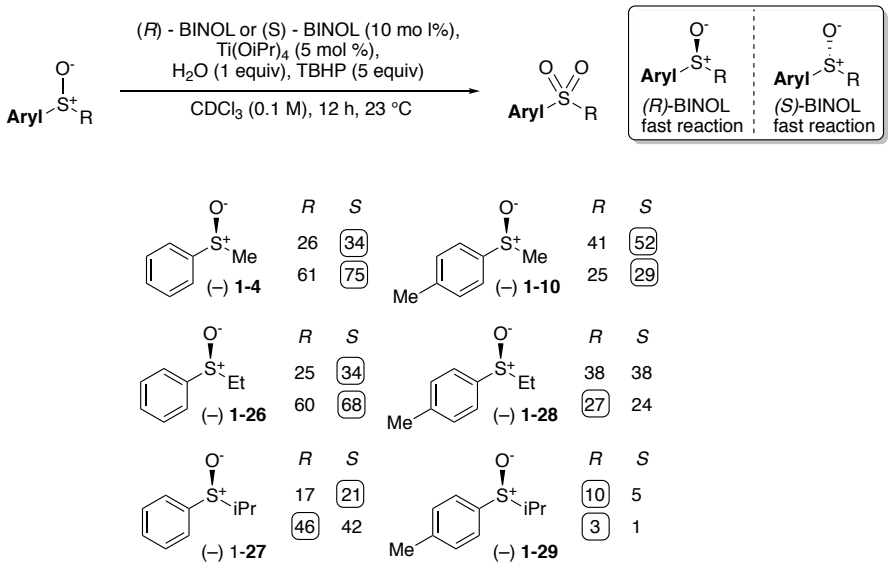
(–) **1-21** was sulfonylated with $MesSO_2Cl$ (**1-22**) to generate sulfonamide **1-23** in 75% yield (Scheme 1-4).[19] Treatment of sulfonamide **23** with thionyl chloride in the presence of 3,5-lutidine generated a highly "endo" selective 96:4 mixture of diastereomeric heterocycles **1-24** and **1-25**, which are epimeric about the sulfur atom. Recrystallization of the major diastereomer from hexanes/ethyl acetate afforded oxathiazolidine-2-oxide **1-24**. Subjecting **1-24** to double nucleophilic displacement using varying organometallic reagents afforded enantiopure sulfoxides while liberating sulfonamide **1-23**, which could be isolated and recycled through the previously described sequence. The opposite enantiomer of each sulfoxide can be synthesized by utilizing the opposite enantiomer of the starting amino indanol, (+) **1-21**. Several enantioenriched substrates have been prepared for use in CEC analysis.



Scheme 1-4. Senanayake protocol for synthesis of enantiopure sulfoxides and scope of enantiopure substrate synthesis ([a] isolated yield after purification [b] determined by chiral HPLC).

1.3.5 Initial CEC Testing of Substrates

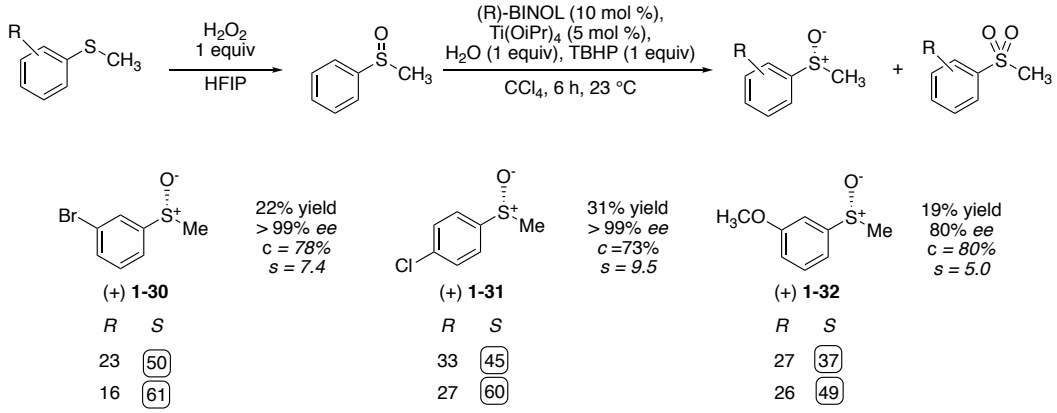
With chiral sulfoxides in hand, the next goal was testing of the optimized CEC conditions in order to validate the mnemonic. Initial results indicate a general lack of selectivity after performing trials with the synthesized substrates in duplicate (Scheme 1-5). Attempts to alter the reaction set-up to facilitate addition of reagents led to varying selectivity. Further attempts to modify reaction conditions led to inconsistent selectivities.



Scheme 1-5. Initial testing of empirically derived mnemonic for CEC method for determination of absolute configuration of sulfoxides. The higher conversion reaction is circled.

Because of these inconsistent results, we chose to further investigate the catalytic system of Uemura by conducting kinetic resolution experiments to assess the selectivity. Treatment of prochiral sulfides with H_2O_2 in HFIP gave the racemic sulfoxides which is then resolved. The resolution experiments yielded the following sulfoxides (**1-30 – 1-32**) in high enantiomeric excess and selectivities on par with those published for similar substrates (Scheme 1-6). Subjecting these chiral sulfoxides to CEC analysis in duplicate afforded results that are in accord with the predicted mnemonic. However, the selectivities in the CEC reactions did not match the selectivities in the

CEC reactions. Further CEC testing of already established substrates once again led to a lack of consistent selectivity. Attempts to change deuterated solvents from chloroform to toluene and dichloromethane were not fruitful in maintaining consistent selectivity. Efforts to alter the equivalents of H_2O to account for the water added from the aqueous TBHP also led to undesired results. As a consequence, the project was not pursued.



Scheme 1-6. Kinetic resolution experiments to investigate selectivity of Uemura system and results of CEC experiments using chiral sulfoxides

1.4 Conclusions

After screening catalyst systems, preliminary results indicate that Uemura's system showed promise for its ability to assign the absolute configuration of sulfoxides via ^{1}H NMR analysis. Optimization of conditions afforded improved selectivity using 5 equivalents of TBHP over a 16.5 hour time period of analysis. Running the reaction in deuterated chloroform allowed for more rapid analysis. Several chiral, enantioenriched sulfoxides were synthesized following Senanayake's protocol. Initial results demonstrated a general lack of selectivity after performing trials with multiple substrates in duplicate. Attempts to alter the reaction set-up or conditions were unsuccessful. Kinetic studies of the Uemura system were conducted in order to better understand it. Ultimately, due to a lack of a consistent, reliable enantioselectivity, this project was not pursued further.

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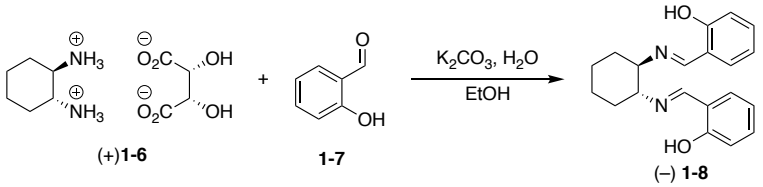
1.6 Experimental Section

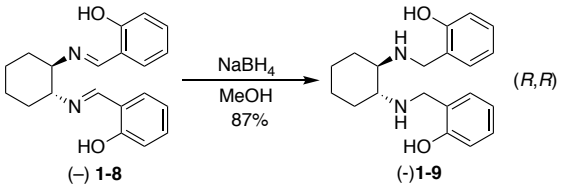
All moisture-sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene (PhMe) were degassed and passed through anhydrous neutral alumina A-2 before use, according to the procedure described by Grubbs.[1] All other chemicals were used as received. Flash chromatography was performed using silicycle 40-63 μm silica gel following the general procedure followed by Still. Proton and carbon NMR spectra measurements were recorded using a Bruker DRX500 with a cryoprobe at 500 MHz for proton and 125 MHz for carbon NMR. Proton NMR shifts are reported as follows: chemical shift (δ) relative to $CDCl_3$ (7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, app. = apparent), coupling constant(s) in Hz, and integrations. Carbon NMR chemical shifts (δ) are reported in parts per million (ppm) and $CDCl_3$ (77.2 ppm) is used as the reference chemical shift. All NMR spectra were processed using MestReNova software. High Resolution Mass Spectrometry (HRMS) were ran by the University of California, Irvine mass spectrometry facility. Optical rotations were taken on a JASCO P-1010 polarimeter using a 50-nm glass cell with a D-line at 589 nm. Electrospray ionization mass spectrometry (ESI-MS) was analyzed on a Waters LCT Class spectrometer in positive mode with flow injection. Enantiomeric excess (*ee*) was determined using chiral HPLC on an Agilent Series 1100 HPLC instrument using Chiralcel OD or OB column with a flow rate of either 0.5 or 1.0 mL/min. with 10-30% isopropanol in n-hexane monitored at 254 nm wavelength. The following formula was used to calculate *ee*: *ee* = (% area of the larger peak) – (% area of the smaller peak). All relevant HPLC traces and NMR spectra can be found in Appendix A.

General scheme for synthesis of salen ligands



A mixture of **(+) 1-6** (8.69 g, 32.9 mmol), K_2CO_3 (4.56 g, 32.9 mmol) and H_2O (22 mL) was stirred until complete dissolution, then MeOH (141 mL) was added. The mixture was heated at 65 °C and a solution of the aldehyde (7.00 mL, 65.8 mmol) in 141 mL of MeOH was added over 30 min. The mixture was refluxed for additional 4 h and was cooled to room temperature. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc, washed with water, dried with Na_2SO_4 and concentrated *in vacuo* to give a crude product. The crude product contained the aldehyde and was used in the next step without purification. ^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound. [2]

The enantiomer (+) **1-8** was prepared in the same manner by substituting (+) **1-6** with its enantiomer (–)-**6** . ^1H, ^{13}C NMR spectra were consistent with those previously reported for this compound.[2]

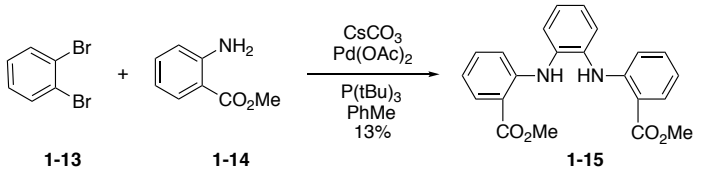


Sodium borohydride (2.61 g, 69.1 mmol) was added portionwise over 40 min to a solution of (–) **1-8** (10.6 g, 32.9 mmol) in 152 mL of MeOH at room temperature and then the reaction mixture was stirred for 1 h under reflux. After cooling to room temperature, 150 mL of H_2O was added and the mixture was extracted with CH_2Cl_2 and concentrated *in vacuo*. If any aldehyde remained

in the starting reaction mixture, the residue was dissolved in aqueous solution of hydrochloric acid (35%) and washed with CH_2Cl_2. Then excess of K_2CO_3 was added to a water phase. The aqueous phase was extracted with CH_2Cl_2, dried, and evaporated to give the product (–) **1-9** in the form of oil. If the product was not sufficiently pure, additional purification by column chromatography was conducted and the product was obtained in the form of an oil. ^1H and ^{13}C NMR were consistent with those previously reported for this compound.[2]

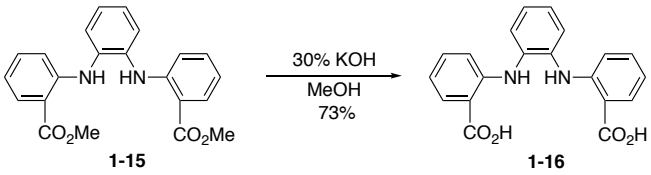
The enantiomer (+) **1-9** was prepared in the same manner by substituting (+) **1-8** with its enantiomer (–)-**8**. ^1H, ^{13}C NMR spectra were consistent with those previously reported for this compound.[2]

General scheme for the synthesis of ligands for Gao catalyst system

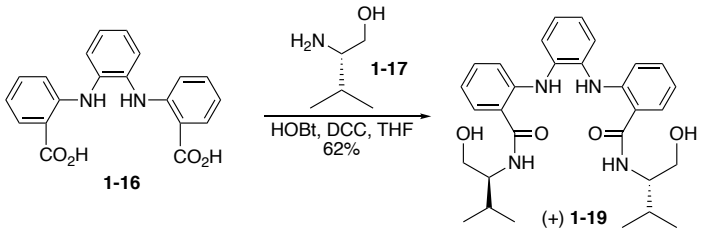


1-13 **1-14** **1-15**

In freshly distilled and degassed toluene (50 mL) was placed $Pd(OAc)_2$ (22.5 mg, 0.100 mmol), under an inert atmosphere. Then tritertbutylphosphine (72 mg, 0.30 mmol) was added and the solution was allowed to stir 10 min. **1-13** (2.36 g, 10.0 mmol), **1-14** (3.63 g, 24.0 mmol) and $CsCO_3$ (10.1 g, 31.0 mmol) were successively added. After overnight reflux, crude mixture was allowed to cool and was then quenched by saturated NH_4Cl (50 mL) solution. Dichloromethane (200 mL) was added and the biphasic mixture separated. The aqueous phase was extracted twice by dichloromethane (60 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes/ethyl acetate 9:1) to afford product **1-15** (0.500 mg, 13%). ^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[3]

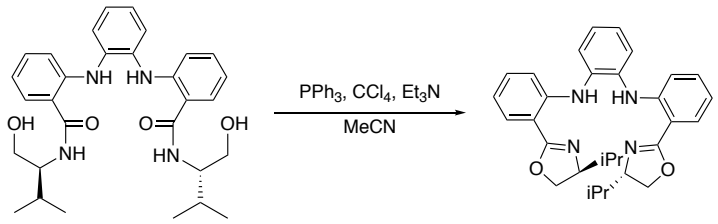


The compound **1-15** (1.98 g, 5.26 mmol) was added to a solution of MeOH (25 mL) and 30% aqueous KOH (25 mL) and stirred at refluxing for 10 h. The resulting mixture was cooled to room temperature, diluted with water (125 mL) and adjusted pH to 4~5 with 6 M HCl and extracted with ethyl acetate (60 mL) three times. The combined organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography in EtOAc to afford product **1-16** (1.34 g, 73%).[1]H and [13]C NMR spectra were consistent with those previously reported for this compound. [3]



A solution of **1-16** (400. mg, 1.15 mmol), DCC (1.04 g, 5.05 mmol), HOBt (341. mg, 2.53 mmol) and **1-17** (260. mg, 2.53 mmol) in dry THF was cooled to –5 °C and stirred for 1 h. After spontaneously warmed to room temperature the mixture was stirred for overnight. The resulting mixture was concentrated under reduced pressure, and the residue was purified by chromatography (hexanes/EtOAc 3:7) to afford (+) **1-19** (371.2 mg, 62%) as a white solid. [1]H and [13]C NMR spectra were consistent with those previously reported for this compound.[3]

The enantiomer (–) **1-19** was prepared in the same manner by substituting **1-17** with its enantiomer, **1-18**). [1]H and [13]C NMR spectra were consistent with those previously reported for this compound.[3]

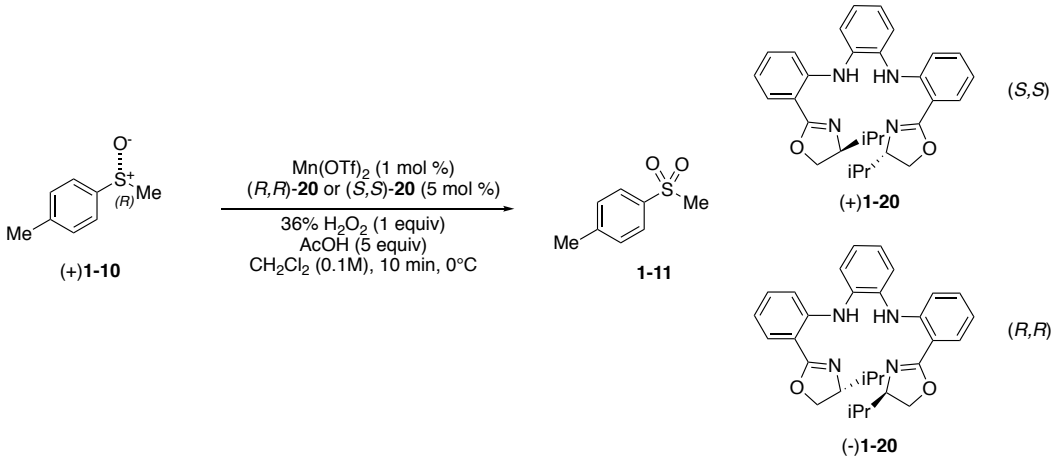


(+)-**16** (+)-**17**

A solution of (+) **1-19** (200. mg, 0.386 mmol), triphenylphosphine (404. mg, 1.54 mmol), triethylamine (215 μL, 1.54 mmol), carbon tetrachloride (149.2 μL, 1.54 mmol) in dry acetonitrile was stirred over night at room temperature. After concentrated in vacuum, the residue was dissolved in dichloromethane, washed with water, dried over anhydrous magnesium sulfate, and then concentrated in vacuum. The crude product was purified by chromatography on silica gel column (ethyl acetate/petroleum ether = 1:3) to afford (+) **1-20** (404.6 mg, 68%) as a yellow solid. ^{1}H and ^{13}C NMR spectra were consistent with those previously reported this compound.[3]

The enantiomer (–) **1-20** was prepared in the same manner by substituting (+) **1-19** with its enantiomer, (–) **1-19.** ^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[3]

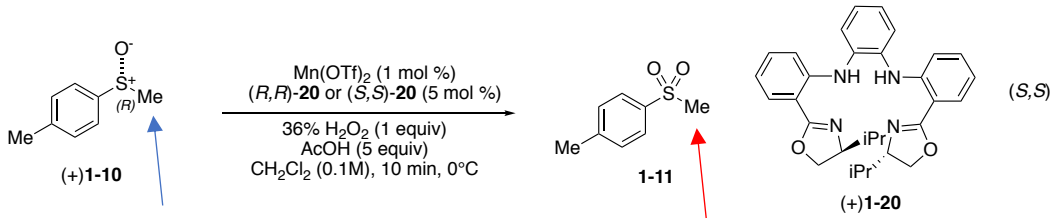
General scheme for CEC conditions utilizing the Gao catalyst system

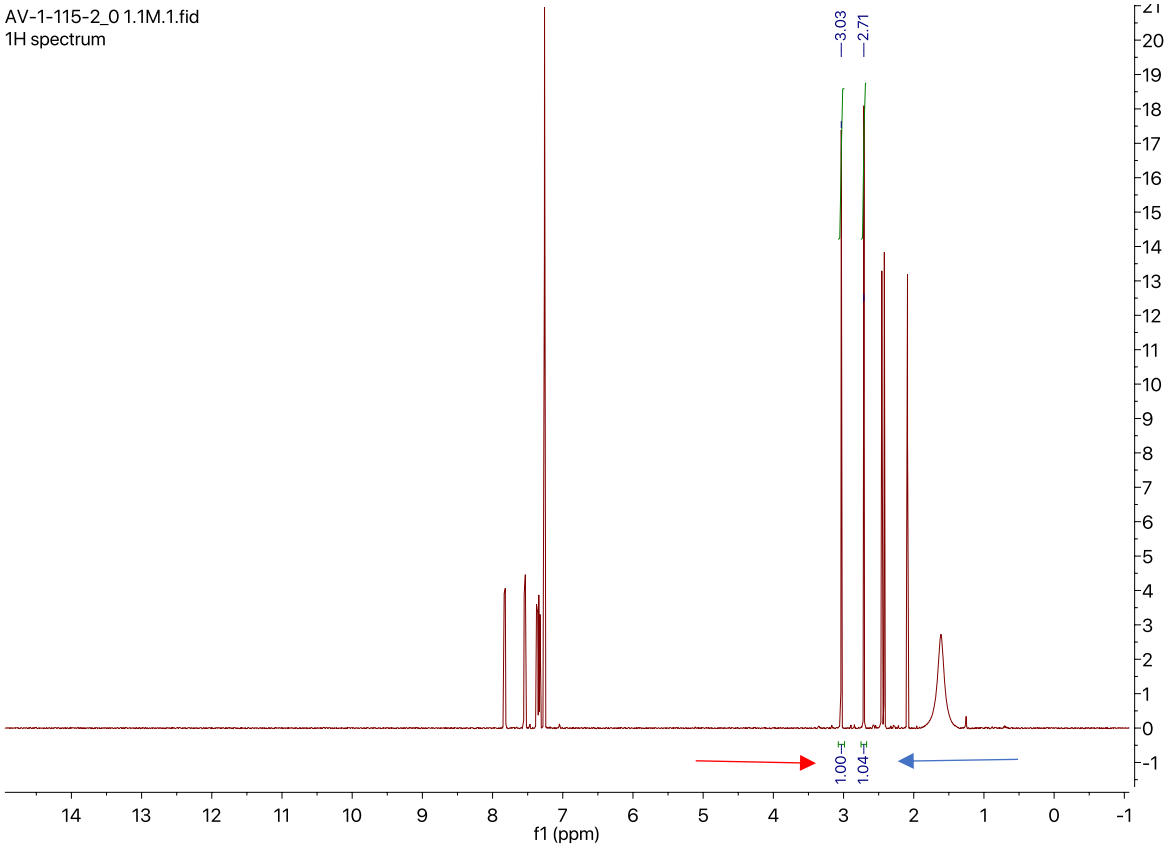


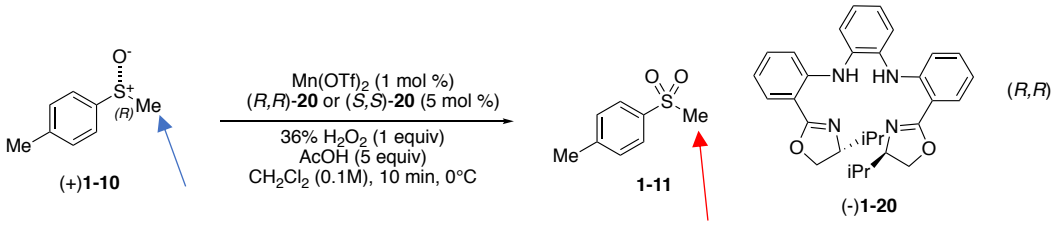
The compound $Mn(OTf)_2$ was weighed into a 5 mL volumetric flask and diluted to volume with CH_2Cl_2 to create a 0.1 M solution. Each ligand ((+)**1-20** and (–) **1-20**) was weighed into separate 2 mL volumetric flasks and diluted to volume to make a 0.1M solution. In two separate dram vials equipped with stir bars were added a 6.5 μL aliquot of the $Mn(OTf)_2$ solution as well as 32.5 μL aliquots of the respective ligands. The mixture was allowed to stir for 4 hours at room temperature. After 4 h, the dram vials were transferred to an ice bath and allowed to cool to 0°C. Once cooled, 10.0 mg of enantiopure sulfoxide (+) **1-10** were accurately weighed and added to each reaction vial. After addition of the sulfoxide, each reaction vial was diluted with was diluted with an additional 502.1 μL and allowed to stir for 10 minutes. After 10 minutes, 18.6 μL of AcOH were added to each vial and allowed to stir for an additional 10 minutes. After 10 minutes, 16.4 μL of 30% H_2O_2 were added to each vial and allowed to stir for 20 minutes. Following 20 minutes, each reaction was taken directly from the vial and passed through a pipette column of $Na_2S_2O_3$. The reactions are then concentrated and diluted with 550 μL of $CDCl_3$ for NMR analysis. A sample CEC analysis is shown below. The location of the methyl peak integrated for analysis is noted. The percent conversion for each reaction was determined as follows:

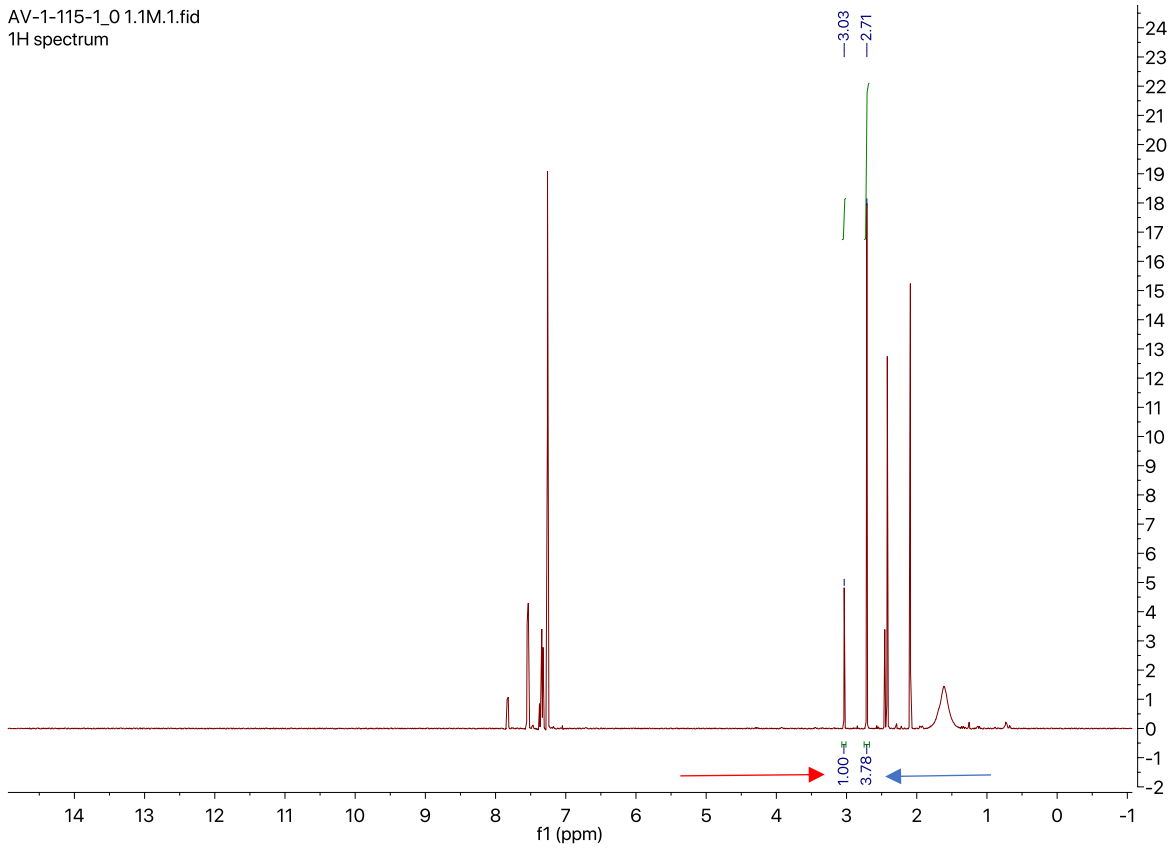
$$\%\ conversion$$

$$= \left(\frac{rel.\ integration\ of\ sulfone\ peak}{rel.\ integration\ of\ sulfone\ peak + rel.\ integration\ of\ sulfoxide\ peak}\right) * 100$$

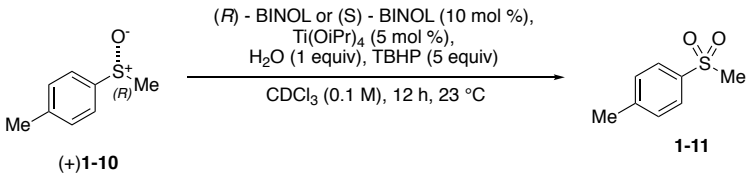








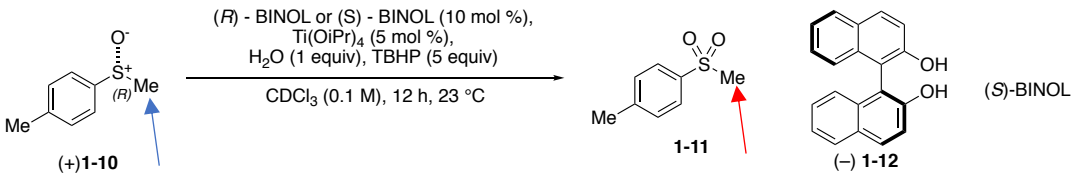
General scheme for CEC conditions utilizing the Uemura catalyst system

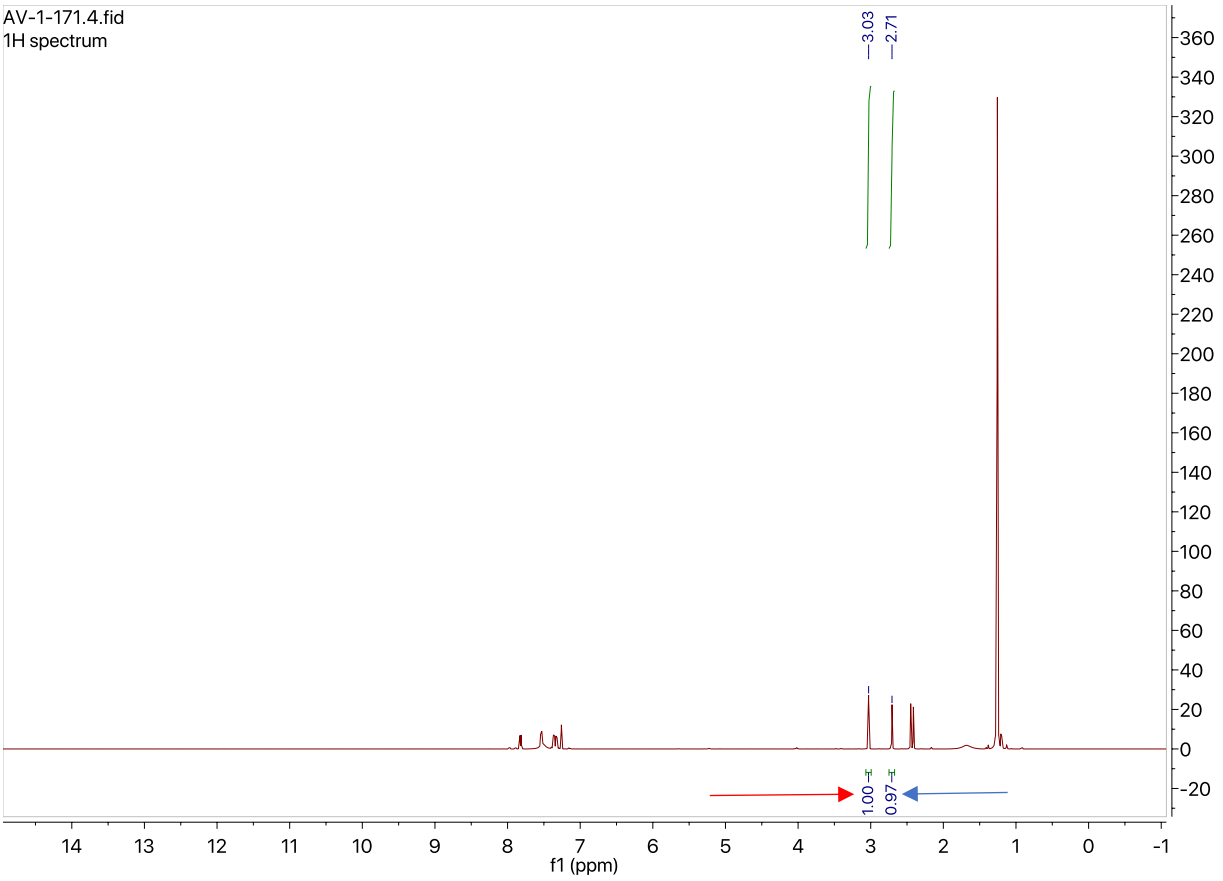


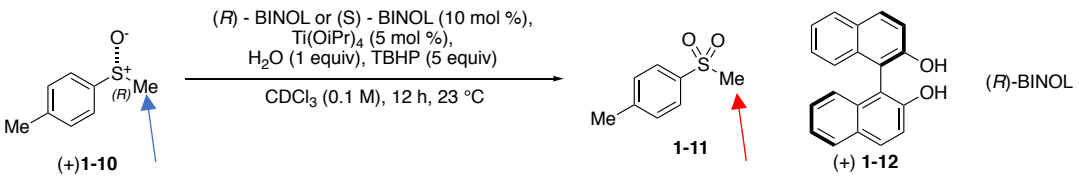
To two separate vials equipped with stir bars was added 3.58 mg of either enantiomer of BINOL, 3.79 µL of $Ti(OiPr)_4$, and 4.5 µL of H_2O. To the vials was added 1 mL of $CDCl_3$ and then added and the pre-catalyst stock solution was added and allowed to stir for one hour. After 1 h, to two separate vials pre-filled with 134.5 µL of $CDCl_3$ was added 40 µL aliquots of the respective pre-

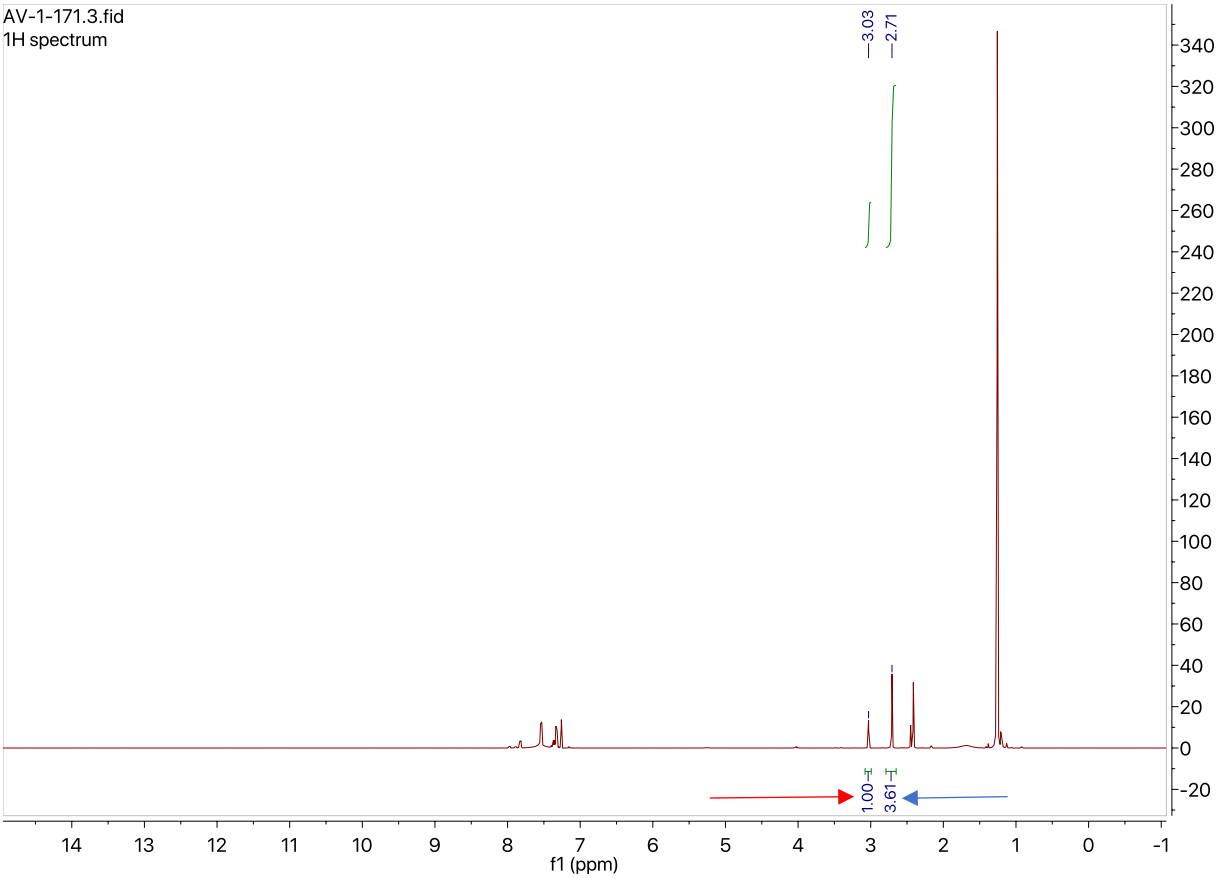
catalyst stock solutions. After addition of the pre-catalyst, a 20 μL aliquot of a 0.5 M solution of (+) **1-10** was then added to both vials and the vials were allowed to sit for 30 minutes. After 30 minutes, TBHP (5.5 μL) was added to each vial and allowed to sit for three hours. After 3 hours, the reaction mixture was directly transferred to an NMR tube and diluted to 550 μL for NMR analysis. A sample CEC analysis is shown below. The location of the methyl peak integrated for analysis is noted. The percent conversion for each reaction was determined as follows:

$$\%\ conversion = \left(\frac{rel.\ integration\ of sulfone\ peak}{rel.\ integration\ of sulfone\ peak + rel.\ integration\ of\ sulfoxide\ peak}\right) * 100$$

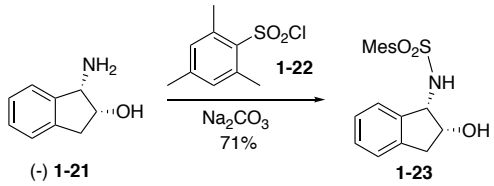

(R) - BINOL or (S) - BINOL (10 mol %),
Ti(OiPr)4 (5 mol %),
H2O (1 equiv), TBHP (5 equiv)
CDCl3 (0.1 M), 12 h, 23 °C
(+)1-10
1-11
(–) 1-12
(S)-BINOL


AV-1-171.4.fid
1H spectrum
3.03
2.71
1.00
0.97
f1 (ppm)



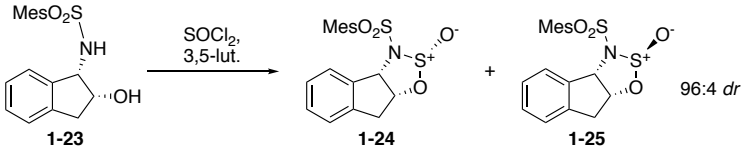


General scheme for synthesis of oxathiazolidine-2-oxide (23)



To a round bottom flask equipped with a magnetic stir bar was added Na_2CO_3 (2.84 g, 26.8 mmol), H_2O (5.8 mL), which was allowed to stir until dissolution. Once dissolved, (–) **1-21** (2.00 g, 13.4 mmol) was added as a solution in 35 mL of EtOAc and the mixture was allowed to stir for 20 minutes. Then, **1-22** (2.84 g, 13 mmol) was added as a solution in 5 mL of EtOAc/THF (1:1). The

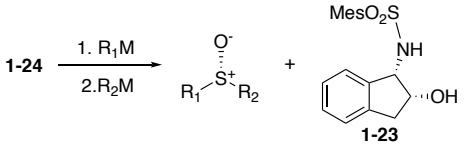
reaction was monitored by thin layer chromatography (TLC) until completion. Once complete, stirring was stopped and layers were allowed to separate. The aqueous phase was then removed and the organic phase was washed with H_2O, 1 M HCl, and H_2O. It was then dried over Na_2SO_4 and concentrated *in vacuo*. The crude material, **1-23,** was carried forward without any further purification. ^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[4]



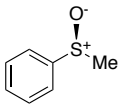
1-23 **1-24** **1-25**

To a flame-dried, 2-neck round-bottom flask fitted with a mechanical stirrer was added **1-23** (2.96 g, 8.93 mmol) in THF (21 mL) and cooled to –45°C. After the reaction mixture was cooled to –45 °C, thionyl chloride (1.02 mL, 13.4 mmol) was added slowly via a syringe in one portion, followed by slow addition of 3,5-lutidine (2.50 mL, 22.1 mmol) in THF (38 mL) over a 30 min period. After the addition was completed, the reaction mixture was stirred, and the reaction was monitored by TLC analysis. Once the reaction was completed, the reaction was quenched with saturated $NaHCO_3$ aqueous solution (30 mL), and the mixture was diluted with ethyl acetate (50 mL) and warmed to ambient temperature with stirring. The phases were allowed to separate and the aqueous phase was removed. The aqueous phase was extracted with ethyl acetate (25 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was added to heptane (75 mL), and the mixture was stirred for 2 h to afford a white to off-white precipitate. The slurry was filtered and the cake was washed with heptane (20 mL). The diastereomeric ratio was 96:4 as determined by ^1H NMR spectroscopy. Crystallization of the crude product from ethyl acetate/hexanes gave diastereopure crystalline **1-24** (2.76 g, 82%). ^1H and ^{13}C NMR were consistent with those previously reported for this compound.[4]

General one-pot procedure for the preparation of sulfoxide:



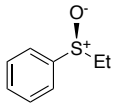
A solution of **1-24** (1.44 g, 3.82 mmol) in THF (10 mL) at –78 °C under argon was added R_1MgCl (1.9 mL, 2.0 M in THF) drop-wise. The reaction mixture was stirred for 1-2 h at –78 °C, and monitored by TLC analysis. Then R_2MgCl (4.5 mL, 1.0 M in THF) was added drop-wise and was monitored by TLC analysis, and quenched by addition of aqueous $NaHCO_3$ (10 mL) and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL), the combined organic phase was washed with 20% NaCl, dried over Na_2SO_4 and evaporated to dryness to give a product and auxiliary mixture that was purified by flash chromatography eluted with EtOAc to afford the sulfoxide.



(-) **1-4**

43% yield, 92% ee

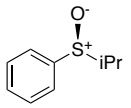
^1H and ^{13}C NMR were consistent with those previously reported for this compound.[4]



(-) **1-26**

50% yield, 93% ee

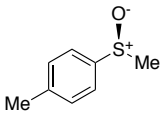
^1H and ^{13}C NMR were consistent with those previously reported for this compound.[4]



(-) 1-**27**

32% yield, 95% ee

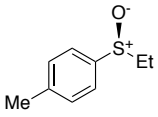
^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[4]



(-) **1-10**

13% yield, 94% ee

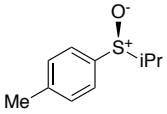
^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[4]



(-) **1-28**

18% yield, 88% ee

^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[4]



(-) **1-29**

49% yield, 95% ee

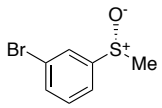
^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[4]

General procedure for the kinetic resolution of sulfoxides utilizing the Uemura system:

To a CCl_4 (2 mL) solution of binaphthol (0.050 mmol) were introduced $Ti(OiPr)_4$ (0.025 mmol) and H_2O (0.50 mmol) using a syringe under ambient atmosphere at room temperature. After the resulting brown solution was stirred magnetically at the same temperature for 1 h, the sulfoxide

(0.50 mmol) was introduced using a syringe at 25 °C. After 0.5 h, 70% aqueous TBHP (0.50 mmol) was introduced using a syringe, and the mixture was stirred for 6-10 h. The reaction mixture was directly submitted to column chromatography to afford the solid chiral sulfoxide (sulfone was eluted first). The *ee* and the configuration of the recovered sulfoxides were determined by HPLC analysis. Selectivity was determined by the following formula.

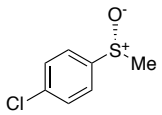
$$s = \frac{\log\left[(1-c)(1-ee)\right]}{\log\left[(1-c)(1+ee)\right]}$$



(+) **1-30**

22% yield, 98% ee

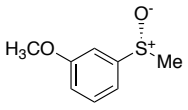
^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[5]



(+) **1-31**

31% yield, > 99% ee

^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[5]



(+) **1-32**

19% yield, 96% ee

^{1}H and ^{13}C NMR were consistent with those previously reported for this compound.[5]

References related to supplementary information:

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Chapter 2. Assigning the Absolute Configuration of Cyclic Secondary Amines Using the Competing Enantioselective Conversion (CEC) Method

2.1 Abstract

Using the kinetic resolution data reported by the Krasnov group, a suitable pseudoenantiomeric acyl chloride bearing substitution along the aromatic ring was synthesized as a potential CEC reagent. Multi-step synthesis of heterocyclic amine substrates bearing varying substitution at the chiral center or aromatic ring was conducted to assess the scope of CEC reactivity. Initial investigations into the CEC reactions displayed mixed results, with a few substrates displaying predicted selectivity and one other displaying the opposite selectivity. Several other substrates did not display any relevant mass peaks (starting material or product) after repeated trials. A base screen showed that the inclusion of tertiary amine bases to the CEC reaction did not influence the selectivity in an appreciable manner.

2.2 Introduction

2.2.1 Importance of Three-Dimensional Configuration

Three-dimensional molecular structure of organic compounds is essential to the chemical reactivity and biological activity of synthetic molecules and natural products. As such, methods that enable determining the absolute configuration of organic molecules are of great interest to chemists in the academic and industrial setting. Current methods to assign absolute stereochemistry include vibrational circular dichroism (VCD), Mosher's method, and X-ray crystallographic analysis.[1]

While these methods described previously are well established and routinely used to assign the absolute configuration of chiral compounds, each has their own limitation. VCD requires significant computational power to generate the theoretical spectra, and experimental spectra often contain instrument or solvent artifacts that complicate analysis. While Mosher's method is commonly performed, it requires a substantial amount of material and requires approximately two days' worth of routine lab work and NMR analysis to complete the assignment of absolute configuration. X-ray crystallography is considered to be the most accurate any small molecules are not crystalline, and the time needed to grow crystals of the proper size, quality, and shape required for analysis can range anywhere from days to weeks. Unfortunately, even with the methods available today, many compounds have been misassigned.[5] Therefore, there is a need for the development of a practical, robust, and rapid method for the assignment of absolute stereochemistry of enantioenriched stereocenters.

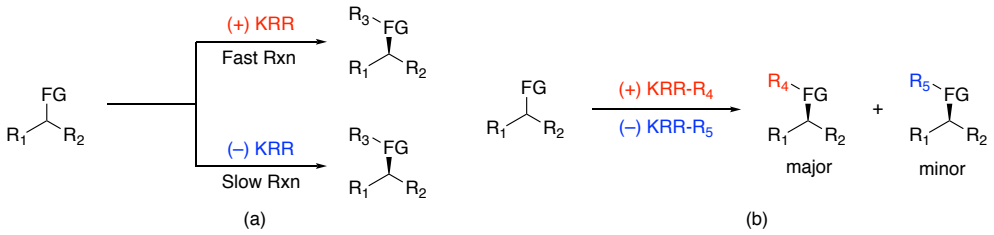


Figure 2-4. Generic examples of the two approaches used in the CEC method to assign absolute configuration of enantiopure substrates. FG = functional group. KRR = kinetic resolution reagent.

2.2.2 Introduction to MS-based CEC Method

The most recent advancement of the CEC method allows for the determination of the absolute configuration of primary and cyclic secondary amine functional groups via a MS-based approach, which uses one flask with two competing pseudoenantiomeric KRR's (pKRRs) present in excess (Figure 2-1, b). Relying on the relative rate of reaction between the two reagents and the substrate, the two pKRRs produce pseudoenantiomeric products, and the ratio of these products can be analyzed via mass spectrometry to identify the fast-reacting, "matched" enantiomer. This MS-based approached is operationally simple, time-efficient, and requires minimal amounts of reagent material, making this a viable alternative to other methods of determination of absolute configuration.

Chiral cyclic amines are common in natural product structures and often associated with biological activity. Chiral cyclic amines are important building blocks in medicinal chemistry. Aside from the physical methods for determining absolute configuration, amines have been analyzed most often by derivatization with chiral reagents.[11] Our laboratory recently reported a CEC method optimized for cyclic amines using pseudoenantiomeric reagents designed around Bode's hydroxamic esters that bears wide substrate scope (Figure 2-2).[10,12]

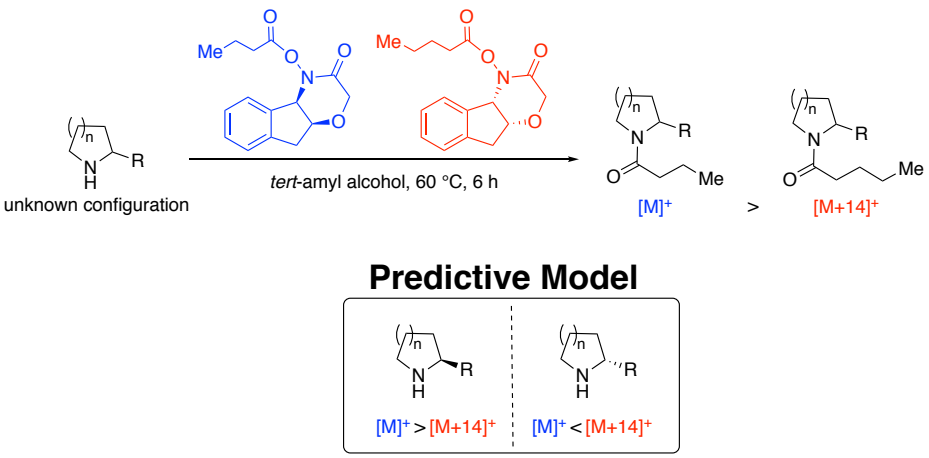


Figure 2-2: CEC method to determine the absolute configuration of cyclic secondary amines using Bode's hydroxamic ester reagent

One significant drawback is the limitation to non-benzannulated amines, due to the lack of nucleophilicity of the aromatic-containing counterpart. A recent report on the acylative kinetic resolution of cyclic amines such as benzoxazines and tetrahydroquinolines was proposed to be a logical start to probe the feasibility of a CEC Method that would expand the substrate scope to these important class of compounds (Figure 2-3).[13]

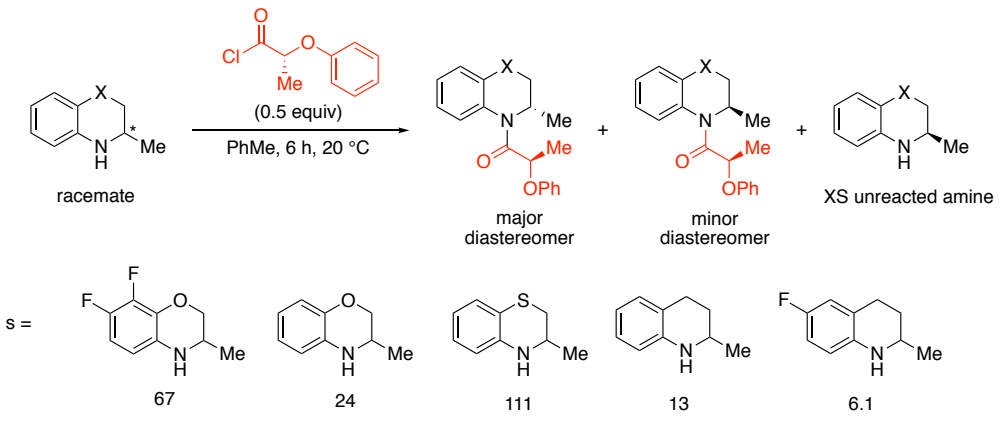
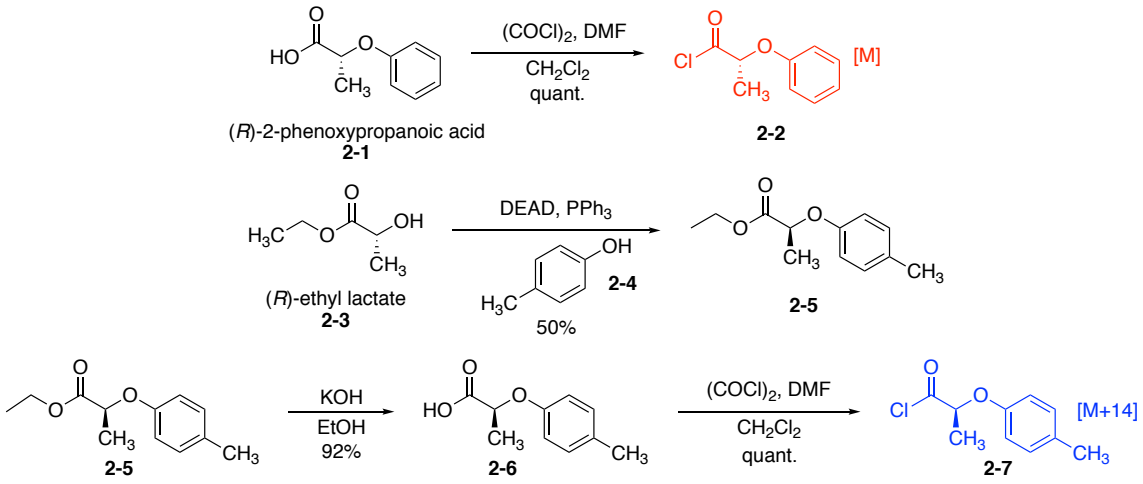


Figure 2-3: Kinetic resolution of benzoxazines and tetrahydroquinolines reported by the Krasnov group

2.3 Results and Discussion

2.3.1 Pseudoenantiomer Reagent Synthesis

With the kinetic resolution data in hand, the next step in developing a CEC methodology was to identify a suitable pseudoenantiomeric acyl chloride for analysis. Acyl chloride **2-2** is readily available from commercially available (*R*)-2-phenoxypropanoic acid (**2-1**). To distinguish the two pseudoenantiomers apart by MS, a tolyl derivative was selected to replace the phenyl derivative found in **2-2**. Synthesis of the pseudoenantiomer begins with Mitsunobu inversion of commercially available (*R*)-ethyl lactate (**2-3**) to install the tolyl fragment (Scheme 2-1). Saponification of the ester (**2-5**) affords carboxylic acid **2-6** which was converted to acyl chloride **2-7** by treatment with oxalyl chloride and DMF.

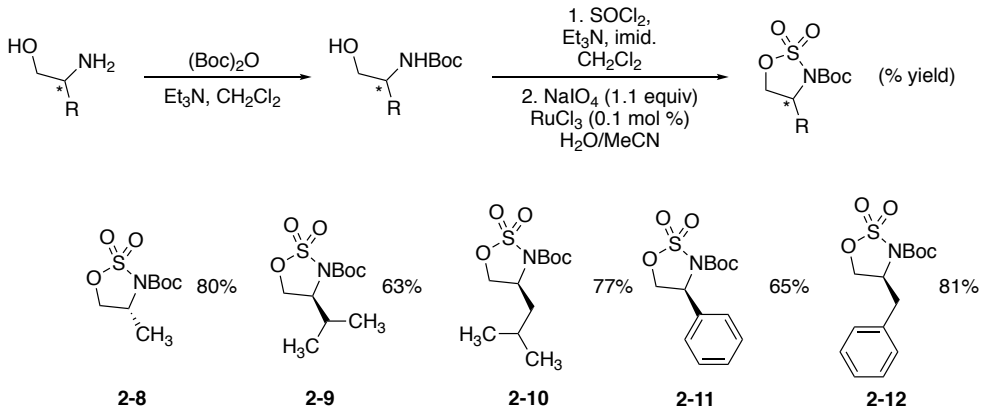


Scheme 2-1: Syntheses of the pseudoenantiomeric acyl chlorides for CEC analysis

2.3.2 Chiral Cyclic Amine Synthesis

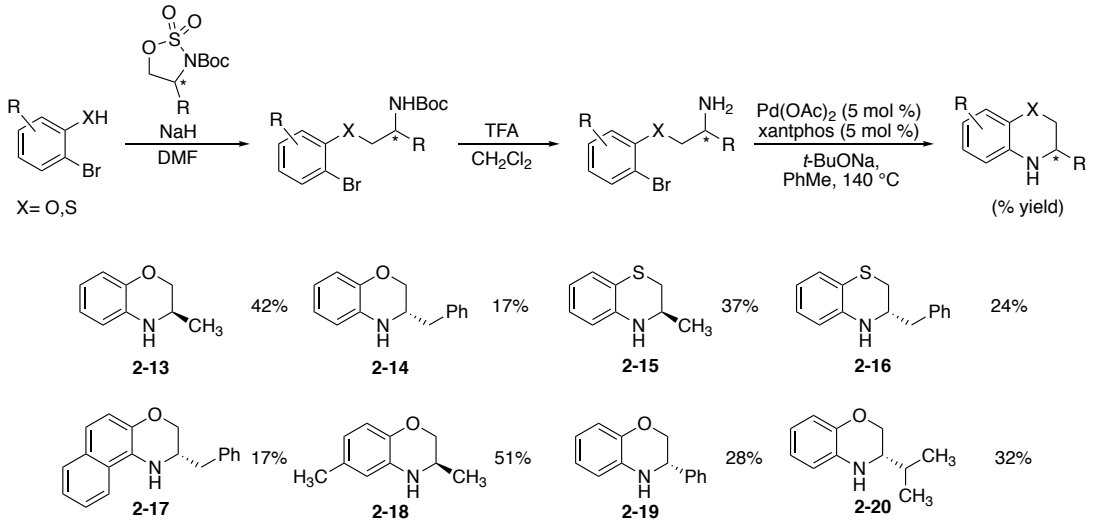
With both acid chlorides in hand, attention was turned to the synthesis of benzoxazine substrates, and other heteroatom analogues. The procedure was a modification of that reported by the Gallagher group (Scheme 2-2).[14] It began with Boc protection of a commercially available amino alcohol, followed by treatment with $SOCl_2$, imidazole, and Et_3N to generate the sulfamidite

product. The sulfamidite was taken on crude to the subsequent oxidation step with $NaIO_4$ and $RuCl_3$ to afford the chiral sulfamidate ring. Aliphatic sulfamidates **2-8** through **2-10** were synthesized as well as aromatic-containing sulfamidates **2-11** and **2-12**.



Scheme 2-2: Synthesis of the chiral sulfamidate rings for heterocyclic amine synthesis

A sulfamidate ring is opened via nucleophilic attack of a phenoxide (or other heteroatom analog) (Scheme 2-3). The amine moiety was deprotected after treatment with TFA. The intermediate was subjected to Buchwald–Hartwig cyclization conditions to yield the desired heterocycle. Benzoxazines **2-13** and **2-14** were synthesized as well as their sulfur analogs, **2-15** and **2-16**. Substrates bearing substitution on the aromatic ring (**2-17** and **2-18**), and those with bulky chiral substituents were also synthesized (**2-19** and **2-20**).



Scheme 2-3: Synthesis of the chiral cyclic amines

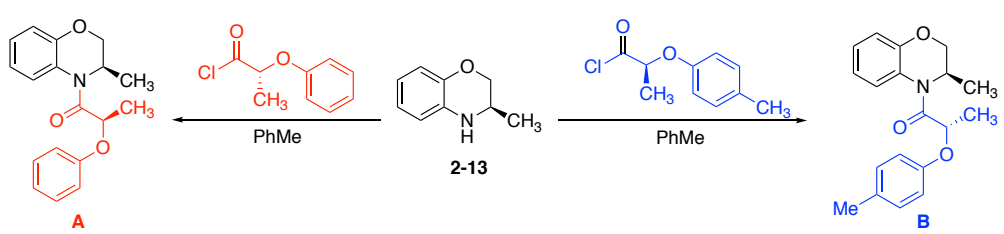
2.3.3 Ionization and Kinetic Control Studies

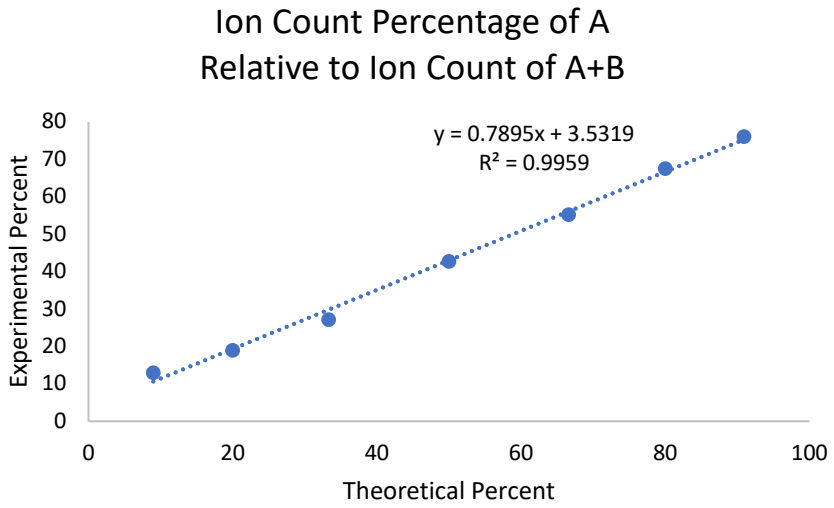
In order to validate the CEC methodology, control experiments need to be performed to verify the reactivity of the two pseudoenantiomers (Scheme 2-4). The first control test, an ionization study (a), was performed in order to verify that both pseudoenantiomers ionize equally upon MS analysis. Benzoxazine **2-13** was derivatized to give both amide products (**A** and **B**) that would result from a CEC experiment, then, solutions of those amide at varying ratios were prepared and then subjected to MS analysis. Ideally, what should be observed from this experiment is an almost 1:1 correlation between the ratios of amides in solution and the ion count ratio of the two amides detected by MS, indicating that both pseudoenantiomers ionize equally. After performing this experiment in duplicate, a slight deviation from 1:1 is seen.

The second control study performed is a test CEC experiment with a racemic benzoxazine **2-13**. Since there is no chirality associated with the substrate, the pseudoenantiomers should not display any selectivity, leading to a 1:1 ion count ratio when analyzed via MS. After performing this experiment in triplicate, what is observed is an average ion count ratio of 51:49. We can conclude that the difference in rate between the two pseudoenantiomeric acyl chlorides is

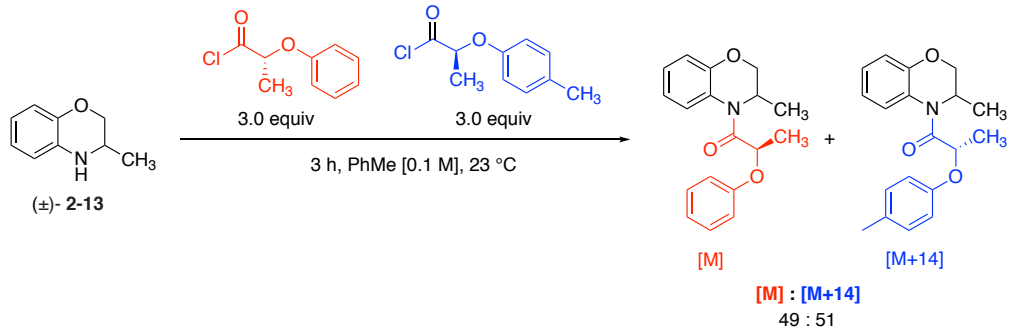
negligible. With the results of the two control studies, the CEC methodology is now poised for initial testing of substrates.

(a)





(b)

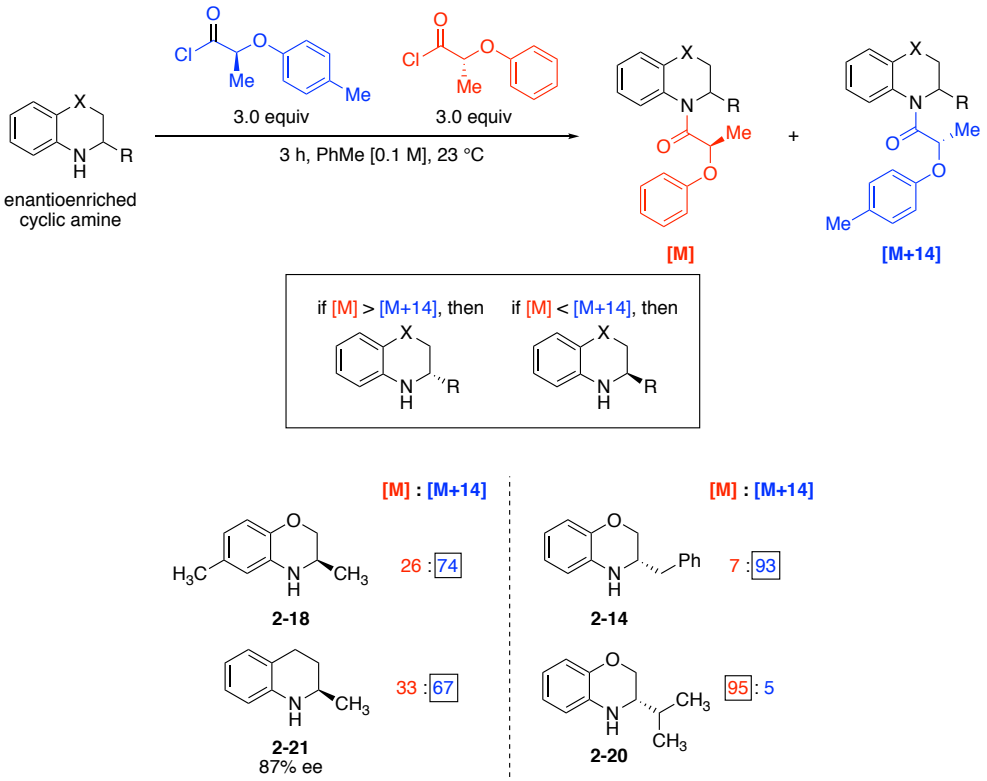


Scheme 2-4: (a) Ionization control study and **(b)** CEC control study in order to verify reactivity of pesudoenantiomers

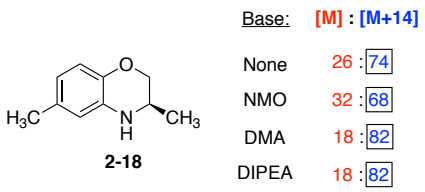
2.3.4 Initial CEC Experiments

Scheme 2-5 shows the initial conditions for the CEC experiment to determine absolute configuration of heterocyclic amines. Based on the results of the kinetic resolution experiments conducted by the Krasnov group, one can make an initial hypothesis for the selectivity of the two pseudoenantiomers. This predictive model (boxed) is the initial one that was tested in order to validate this CEC experiment.

(a)

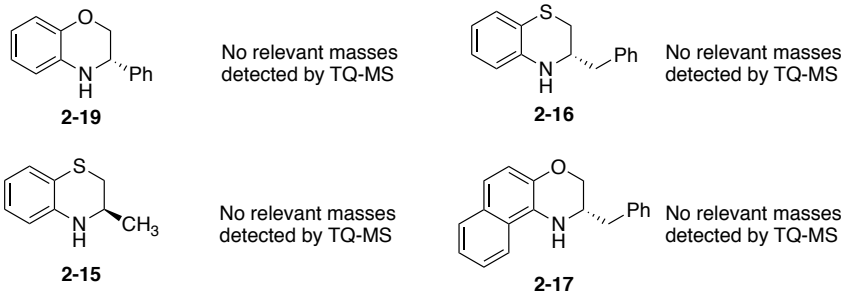


(b)



Scheme 2-5: (a) Initial CEC experiments to determine absolute configuration of cyclic amines. **(b)** Base screen of CEC experiment

Initial results with substrate **2-18** and chiral tetrahydroquinoline **2-21** conveniently available in our laboratory displayed selectivity that is in agreement with the predictive model. However, substrates with bulker substituents at the chiral position displayed mixed results. Benzyl substituted benzoxazine **2-14** displayed opposite selectivity whereas substrate **2-20** behaved as expected. In all cases, there was full conversion after three hours as monitored by TLC. In attempt to increase the selectivity of this CEC reaction, a base screen using substrate **2-18** was conducted by adding one equivalent of various tertiary amine bases to the different CEC reactions (Scheme 2-5, b). Upon analysis, it was shown that in all cases, the observed selectivity still matched the predicted selectivity. The addition of *N*-methylmorpholine (NMO) slightly decreased the selectivity whereas the addition of both *N,N*-dimethylaniline (DMA) and diisopropylethylamine (DIPEA) increased the selectivity, to a small extent. Unexpectedly, several substrates did not display any relevant mass peaks (amine starting material or amide product) after repeated subjection to CEC trials (Scheme 2-6). Attempts to isolate and characterize the products from these reactions via chromatography and recrystallization proved to be difficult.



Scheme 2-6: Substrates that did not display any relevant mass peaks during CEC analysis.

2.4 Conclusions

Based on data for the kinetic resolution of cyclic secondary amines reported by the Krasnov group, a suitable pseudoenantiomeric acyl chloride was synthesized and verified for CEC analysis via ionization and kinetic control studies. Multistep synthesis of benzoxazines and sulfur analogs

for testing was performed via a modified route of a literature-known procedure. Initial testing of substrates provided mixed results, with one substrate demonstrating inversion of predicted selectivity while a few others did not display any relevant mass peaks after CEC testing. A base screen was conducted, and was found to have no significant impact on selectivity.

2.5 References

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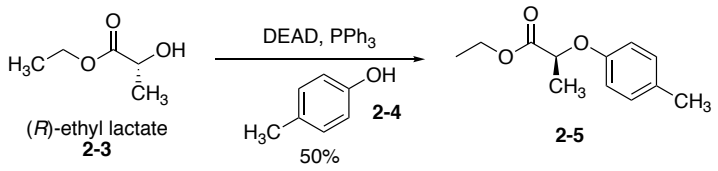
2.6 Experimental

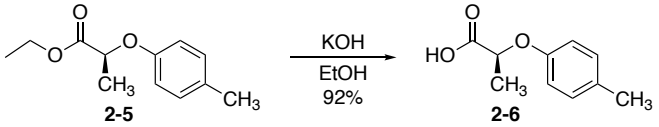
All moisture-sensitive reactions were carried out in flame- or oven-dried glassware under argon atmosphere. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene (PhMe) were degassed and passed through anhydrous neutral alumina A-2 before use, according to the procedure described by Grubbs.[1] All other chemicals were used as received. Flash chromatography was performed using silicycle 40-63 μm silica gel following the general procedure followed by Still. Proton and carbon NMR spectra measurements were recorded using a Bruker DRX500 with a cryoprobe at 500 MHz for proton and 125 MHz for carbon NMR. Proton NMR shifts are reported as follows: chemical shift (δ) relative to $CDCl_3$ (7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, app. = apparent), coupling constant(s) in Hz, and integrations. Carbon NMR chemical shifts (δ) are reported in parts per million (ppm) and $CDCl_3$ (77.2 ppm) is used as the reference chemical shift. All NMR spectra were processed using MestReNova software. High Resolution Mass Spectrometry (HRMS) were ran by the University of California, Irvine mass spectrometry facility. Optical rotations were taken on a JASCO P-1010 polarimeter using a 50-nm glass cell with a D-line at 589 nm. Electrospray ionization mass spectrometry (ESI-MS) was analyzed on a Waters LCT Class spectrometer in positive mode with flow injection. Enantiomeric excess (*ee*) was determined using chiral HPLC on an Agilent Series 1100 HPLC instrument using Chiralcel OD column with a flow rate of either 0.5 or 1.0 mL/min. with 10% isopropanol in n-hexane monitored at 254 nm wavelength. The following formula was used to calculate *ee*:
ee = (% area of the larger peak) – (% area of the smaller peak). All relevant HPLC traces and NMR spectra can be found in Appendix B.

Scheme for synthesis of pseudoenantiomer



A mixture of **2-3** (200. mg, 1.69 mmol**)**, PPh_3 (443. mg, 1.69 mmol**)**, and **2-4** (183. mg, 1.69 mmol**)** were dissolved in THF in a flame-dried round bottom flask. This reaction was allowed to stir at room temperature for 20 minutes. A solution of DEAD (324. mg, 1.86 mmol**)** in THF was then added dropwise and left to stir at room temperature. The reaction was monitored to completion by TLC. Once complete, The THF was evaporated and diethyl ether, or a mixture of diethyl ether and hexane, was added in order to precipitate the formed triphenylphosphine oxide, which was filtered off. This procedure was repeated several times. The crude product was loaded on silica gel and purified by silica gel chromatography to yield 6 as an off-yellow oil (175.8 mg, 50% yield).

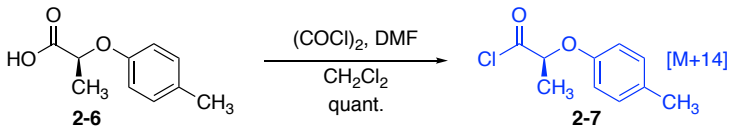
^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[2]



A solution of **2-5** (305. mg, 1.47 mmol) in EtOH was added to an aqueous solution of KOH (1.25 M, 5.64 mL) at 0 °C and allowed to warm to room temperature while stirring until complete. The reaction was then acidified with 3 M HCl to pH 3 and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous sodium sulfate and concentrated under vacuum to yield **2-6** as a white solid (185.3 mg, 70% yield).

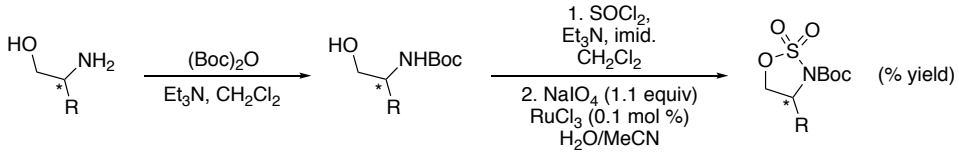
^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[2]

ee (> 99%) was determined using literature known conditions.[2]



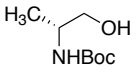
Oxalyl chloride (35.6 µL, 0.415 mmol) was added to a solution of acid **2-6** (0.30 mg, 0.17 mmol) and DMF (1 drop) in CH_2Cl_2. The reaction mixture was stirred at room temperature for 6 h, and then evaporated to dryness under reduced pressure. The residue was dried over P_2O_5 in vacuo to afford compound **2-7** quantitatively as a yellowish oil, which had an unpleasant odor. The NMR spectrum was identical to that published for racemic chloride **2-7**.[3]

General scheme for synthesis of chiral sulfamidate ring



Boc protection

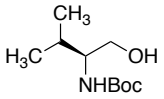
To a solution of chiral amino alcohol (1.0 equiv) and Et_3N (1.0 equiv) in CH_2Cl_2 (0.33 M) was added Boc_2O (1.0 equiv). This solution was stirred at room temperature and monitored to completion by TLC. Once complete, the reaction is quenched with addition of 1 M HCl. Extract 3X's with CH_2Cl_2, wash with brine, dry over anhydrous sodium sulfate, and then concentrated in vacuo. The crude material is then purified to yield the Boc-protected amino alcohol product.



S 2-1

2.46 g, 87% yield

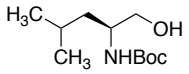
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[4]



S 2-2

2.80 g, 95% yield

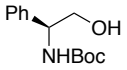
^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[4]



S 2-3

193.6 mg, 61% yield

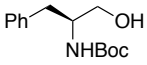
^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[4]



S 2-4

389.7 mg, 75% yield

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[5]



S 2-5

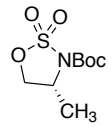
2.82 g, 85% yield

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[4]

Sulfamidate formation

To a cooled (–50 °C) solution of $SOCl_2$, imidazole, and Et_3N in anhydrous CH_2Cl_2 (57 mL) was added dropwise, a solution of N-Boc amino alcohol in anhydrous CH_2Cl_2 over 0.5 h. The mixture was then warmed to 0 °C allowed to stir, and monitored by TLC. Once reaction is complete water is added to the reaction and allowed to stir for 5 minutes. The organic portion was isolated, washed with brine, dried and concentrated in vacuo to afford intermediate cyclic sulfamidite as a colorless oil. This material was used immediately in the next stage without further purification. To an ice-

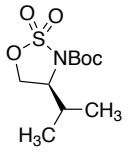
cooled (0 °C) solution of intermediate cyclic sulfamidite in MeCN was added sequentially $NaIO_4$, $RuCl_3$ and then water. The mixture was stirred at 0 °C until complete by TLC and then diluted with water and extracted (2 x Et_2O). The organic extracts were combined, washed with water, and then brine, dried with Na_2SO_4 and concentrated in vacuo. The residue was filtered through a pad of silica (eluting with Et_2O) to afford cyclic sulfamidate product a colorless, crystalline solid.



2-8

3.05 g, 92% yield

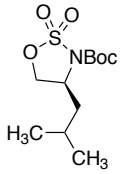
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[6]



2-9

200.2 mg, 74% yield

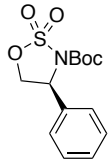
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[6]



2-10

193.6 mg, 78% yield

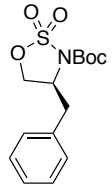
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[6]



2-11

304.3 mg, 76% yield

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[6]

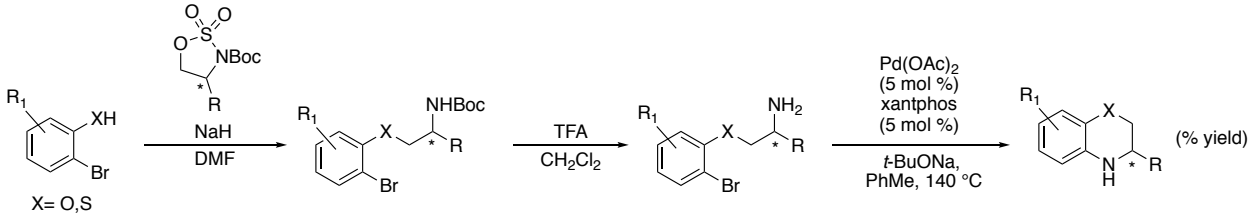


2-12

3.14 g, 90% yield

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[6]

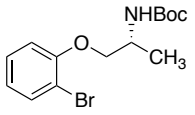
General scheme for synthesis of chiral amine heterocycle



Ring-Opening

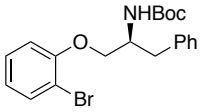
To a solution of 2-bromophenol (or thiophenol) (1.5 equiv) in anhydrous DMF was added NaH (1.5 equiv, 60 % dispersion in mineral oil) and the mixture was stirred at room temperature for 15 minutes. Cyclic sulfamidate (1.0 equiv) was added and the mixture was stirred at room temperature and monitored by TLC until completion. Once complete, aq. 5 M HCl is added and the reaction is allowed to stir for 2 h. The reaction mixture is then diluted with aq. 1 M NaOH and extracted (3 x Et_2O). The organic extracts were combined, washed (3 x 1 M NaOH), dried with anhydrous

Na_2SO_4 and concentrated in vacuo. The crude mixture is taken forward without any further purification.



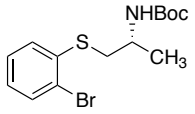
S 2-6

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[7]



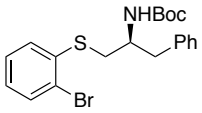
S 2-7

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[7]



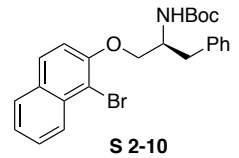
S 2-8

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification. [8]



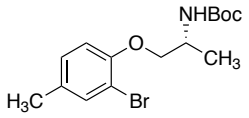
S 2-9

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[8]



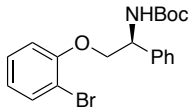
S 2-10

Crude ^{1}H and ^{13}C NMR spectra were consistent with structure, material carried through without further purification.



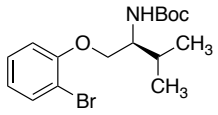
S 2-11

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[7]



S 2-12

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[7]



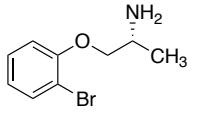
S 2-13

Crude ^{1}H and ^{13}C NMR spectra were consistent with structure, material carried through without further purification.

Boc Deprotection

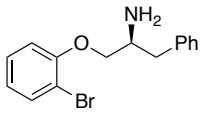
To a vial of crude Boc-protected material was added CH_2Cl_2 (0.25 M) and allowed to stir until dissolution at which point an excess of TFA was added. The reaction was monitored by TLC until completion at which point it was cooled to 0 °C and quenched by addition of 4 M NaOH until basic. The reaction mixture is then extracted (3 x DCM). The organic layer was washed with water,

brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford a crude mixture of product. The crude mixture was taken forward without any further purification.



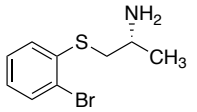
S 2-14

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[8]



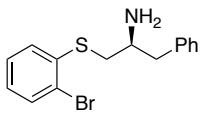
S 2-15

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[8]



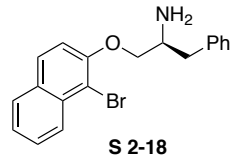
S 2-16

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[9]



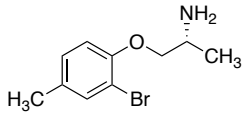
S 2-17

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[9]



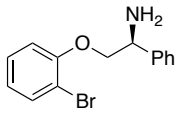
S 2-18

^{1}H and ^{13}C NMR spectra were consistent with structure. Material carried through without further purification.



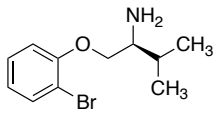
S 2-19

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[8]



S 2-20

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound, material carried through without further purification.[9]



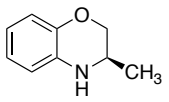
S 2-21

^{1}H and ^{13}C NMR spectra were consistent with structure, material carried through without further purification

Buchwald–Hartwig Cyclization

To a flame-dried Schlenk flask capped with a rubber septa was charged, $Pd(OAc)_2$ (0.05 equiv), xantphos (0.05 equiv), and NaOtBu (1.5 equiv). In a separate, degassed vial with crude amine material was added PhMe and the solution was transferred to the Schlenk flask via syringe addition. The rubber septa is replaced with a glass stopper and sealed with Teflon tape. The reaction is then transferred to a sand bath and heated to 140 °C for 24 h. The reaction The mixture

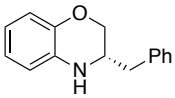
was cooled to r.t., diluted with EtOAc, washed with water and then brine, dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (10% EtOAc in hexanes) to afford amine product.



2-13

33.7 mg, 55% yield

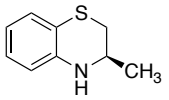
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[9]



2-14

17.0 mg, 25% yield

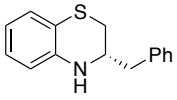
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[10]



2-15

14.4 mg, 22% yield

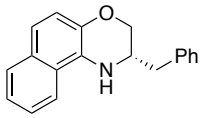
^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[8]



2-16

30.7 mg, 57% yield

^1H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[9]

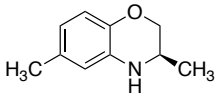


2-17

32.7 mg, 42% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.34 – 7.22 (m, 6H), 7.09 (d, *J* = 8.8 Hz, 1H), 4.36 (dd, *J* = 10.5, 2.6 Hz, 1H), 4.08 (dd, *J* = 10.6, 6.6 Hz, 1H), 3.77 (q, *J* = 7.0, 6.4 Hz, 1H), 3.04 – 2.84 (m, 2H).

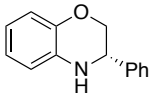
^{13}C NMR (126 MHz, $CDCl_3$) δ 129.45, 129.00, 128.70, 127.03, 125.43, 123.69, 118.79, 118.58, 68.90, 51.37, 38.76.



2-18

24.7 mg, 58% yield

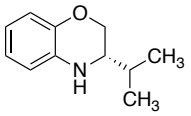
^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[7]



2-19

16.0 mg, 80% yield

^{1}H and ^{13}C NMR spectra were consistent with those previously reported for this compound.[10]



2-20

33.0 mg, 56% yield

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 – 6.73 (m, 1H), 6.69 – 6.58 (m, 1H), 4.26 (dd, J = 10.6, 2.8 Hz, 1H), 3.97 (dd, J = 10.6, 7.5 Hz, 1H), 3.13 (td, J = 7.2, 2.7 Hz, 1H), 1.84 – 1.73 (m, J = 6.8 Hz, 1H), 1.03 (dd, J = 13.4, 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.04, 133.86, 121.45, 118.57, 116.49, 115.37, 67.74, 55.34, 29.99, 29.84, 18.78, 18.64.

CEC General Reaction Procedure

The respective amine was weighed into a volumetric flask and diluted to volume with the CH_2Cl_2 to make a 0.1 M stock amine solution. Each acyl transfer reagent precursor (**2-1** and **2-6**) was weighed into separate volumetric flasks and diluted to volume with to make stock volumetric solutions. The appropriate amount of each acyl transfer reagent precursor solution was added to a single separate volumetric flask and diluted to volume with CH_2Cl_2 in order to make a 0.25M one to one molar equivalent solution of each acyl transfer reagent.

To a round bottom sealed with a rubber septa was added the appropriate amount of acyl transfer reagent solution, $(COCl)_2$ (6 equiv), and 1 drop of DMF. The reaction mixture was stirred at room temperature for 2 hours, and then evaporated to dryness under reduced pressure. The appropriate amount of amine solution is then added to the round-bottom flask and the reaction is monitored to completion by TLC. Once the reaction is complete, the reaction is quenched with the addition of 10 equivalents of 1M NaOH and allowed to stir for 15 minutes. The organic layer is taken and diluted to 10 mM and a 75 μL aliquot of the mixture is taken and added to a amber mass spectrometry vial containing 325 μL of methanol. The contents of the vial were mixed and the sample was analyzed by ESI-MS. In each case, the ion counts of the corresponding protonated and sodiated peaks were analyzed. In cases where the sodiated or protonated peaks overlapped with another component in the mixture, only the non-overlapping peaks (H^+ or Na^+) was used in the analysis. The peaks corresponding to the [M+H] and [M+Na] for each amide is shown. The ion count (second number above each peak) is summed for each amide product and the ratio is calculated.

References related to supplementary information:

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rose, R. K.; Timmers, F.J. *Organomettalics* **1996,** *15,* 1518 – 1520.

(2) Kato, D.; Mitsuda, S.; Ohta, H. *J. Org. Chem.* **2003**, *68*, 7234 – 7242.

(3) Liu, M.-Y.; Shi, D.-Q. *Journal of Heterocyclic Chemistry* **2014**, *51*, 432 – 435.

(4) Reddy Guduru, S. K.; Chamakuri, S.; Raji, I. O.; MacKenzie, K. R.; Santini, C.; Young, D. W. *J. Org. Chem.* **2018**, *83*, 11777 – 11793.

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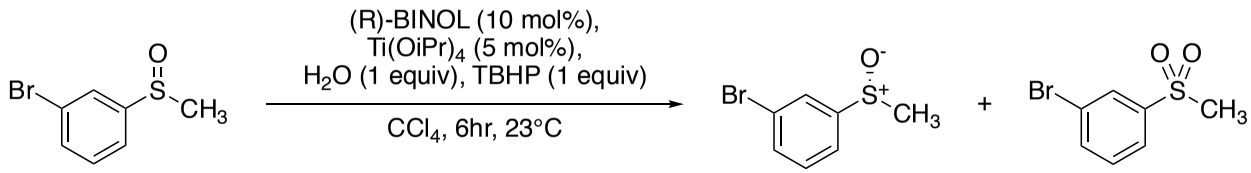
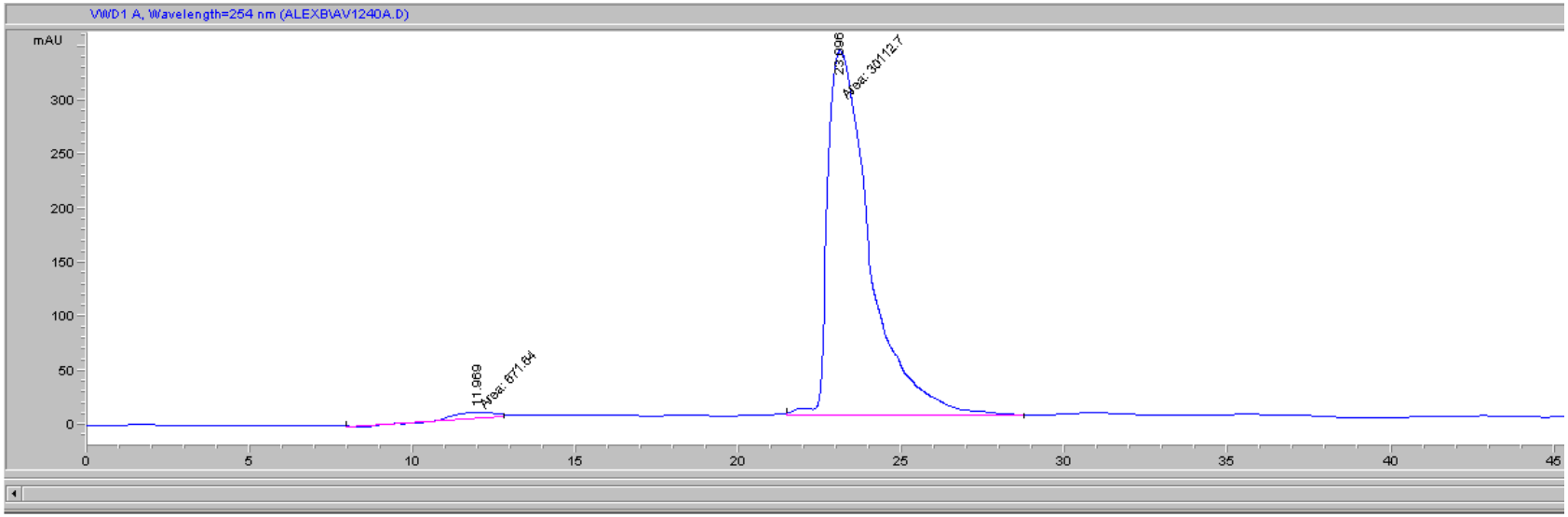
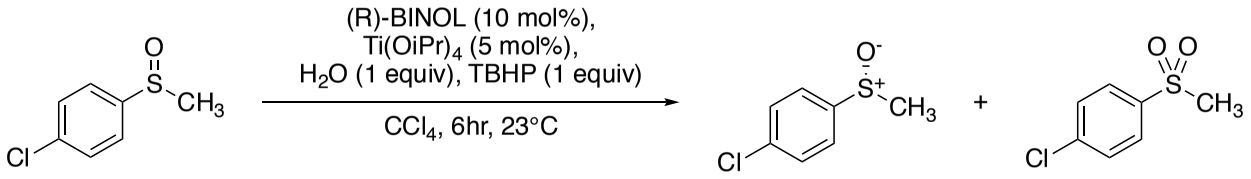
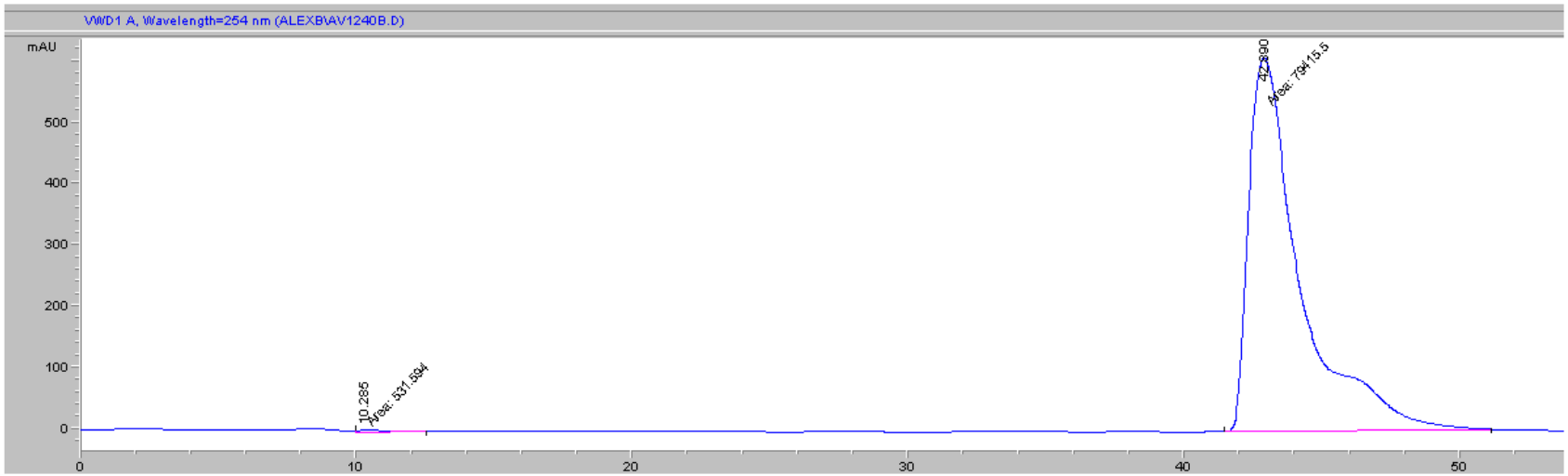
Appendix A:

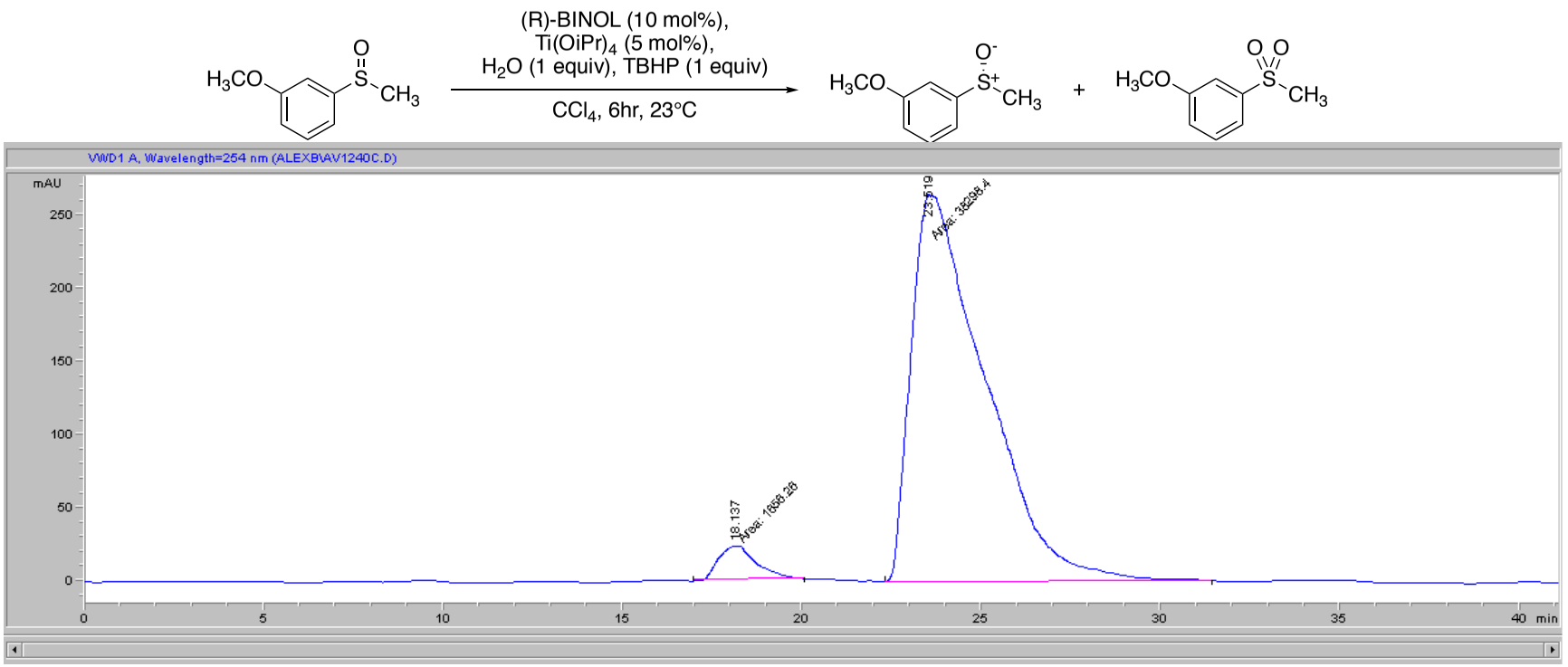
HPLC Traces of Resolved Sulfoxides for Chapter 1


(R)-BINOL (10 mol%),
Ti(OiPr)4 (5 mol%),
H2O (1 equiv), TBHP (1 equiv)
CCl4, 6hr, 23°C
Br
O
S
CH3
O-
S+
O O


VWD1 A, Wavelength=254 nm (ALEXB\AV1240A.D)
mAU
300
250
200
150
100
50
0
11.969
Area: 671.84
23.696
Area: 30112.7
0
5
10
15
20
25
30
35
40
45

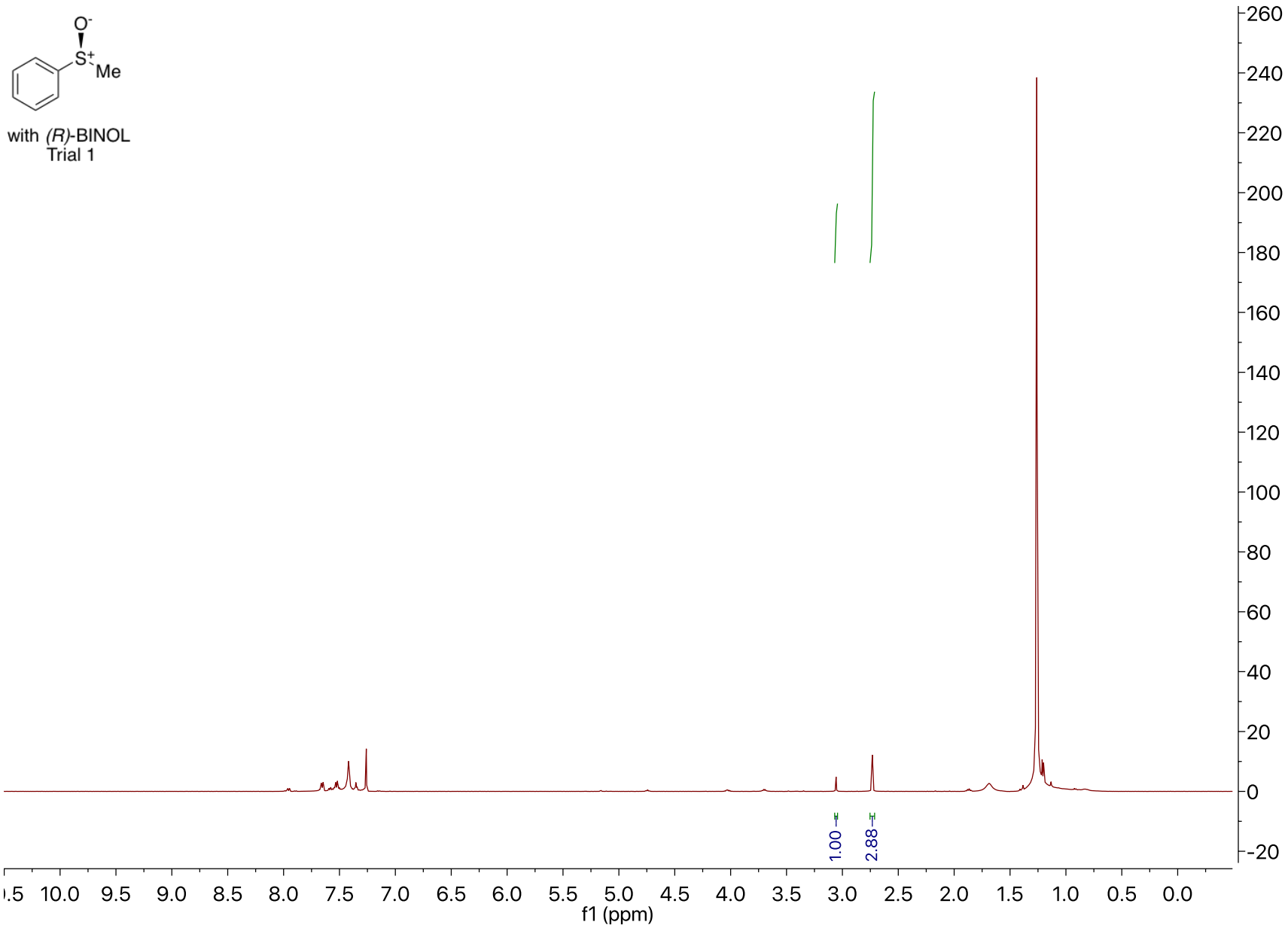

(R)-BINOL (10 mol%),
Ti(OiPr)4 (5 mol%),
H2O (1 equiv), TBHP (1 equiv)
CCl4, 6hr, 23°C
Cl
CH3
+


VWD1 A, Wavelength=254 nm (ALEXB\AV1240B.D)
mAU
500
400
300
200
100
0
10.285
Area: 531.594
42.690
Area: 794 15.5
0
10
20
30
40
50

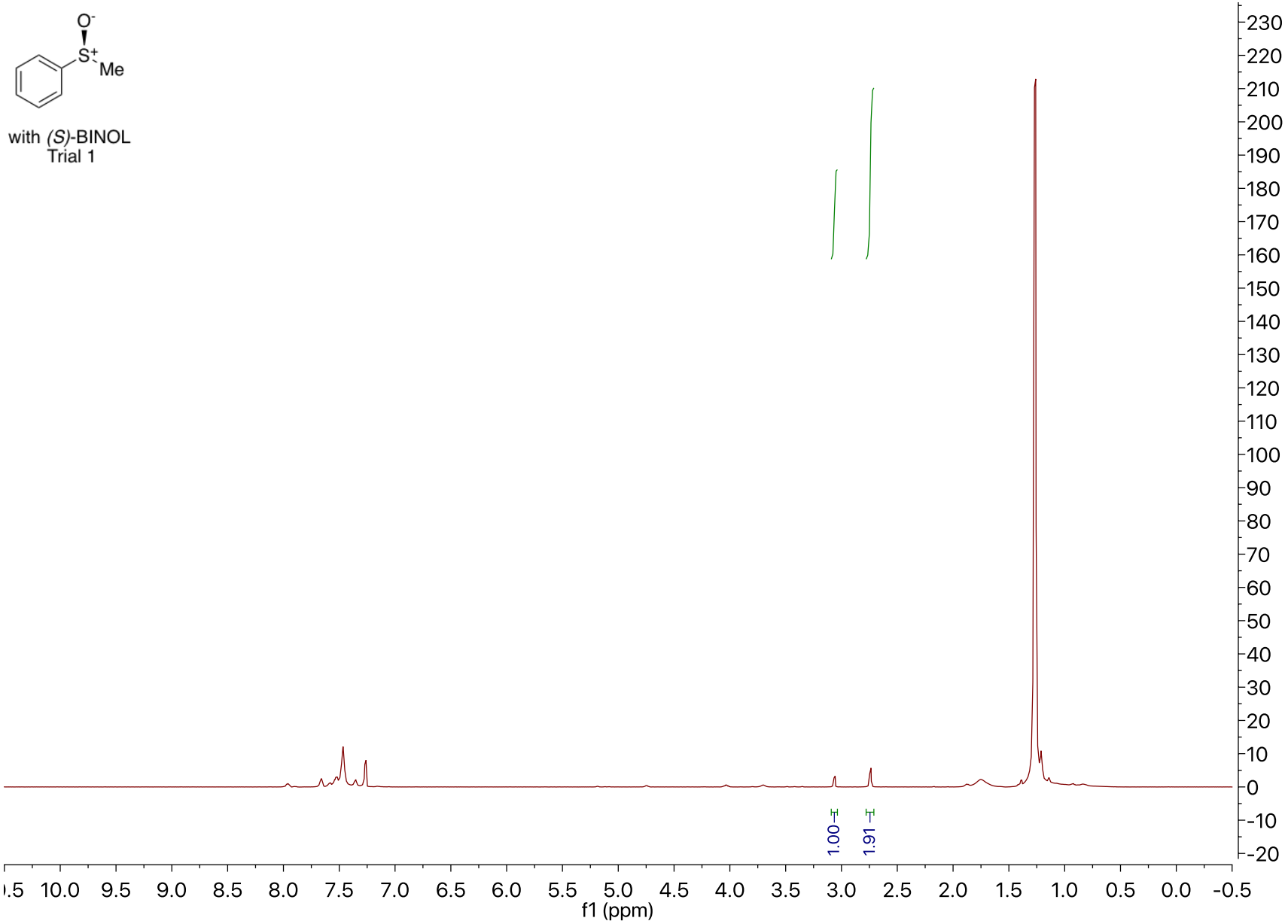

(R)-BINOL (10 mol%),
Ti(OiPr)4 (5 mol%),
H2O (1 equiv), TBHP (1 equiv)
CCl4, 6hr, 23°C
H3CO
CH3
+
VWD1 A, Wavelength=254 nm (ALEXB\AV1240C.D)
mAU
250
200
150
100
50
0
18.137
Area: 1658.28
23.519
Area: 35298.4
0
5
10
15
20
25
30
35
40 min

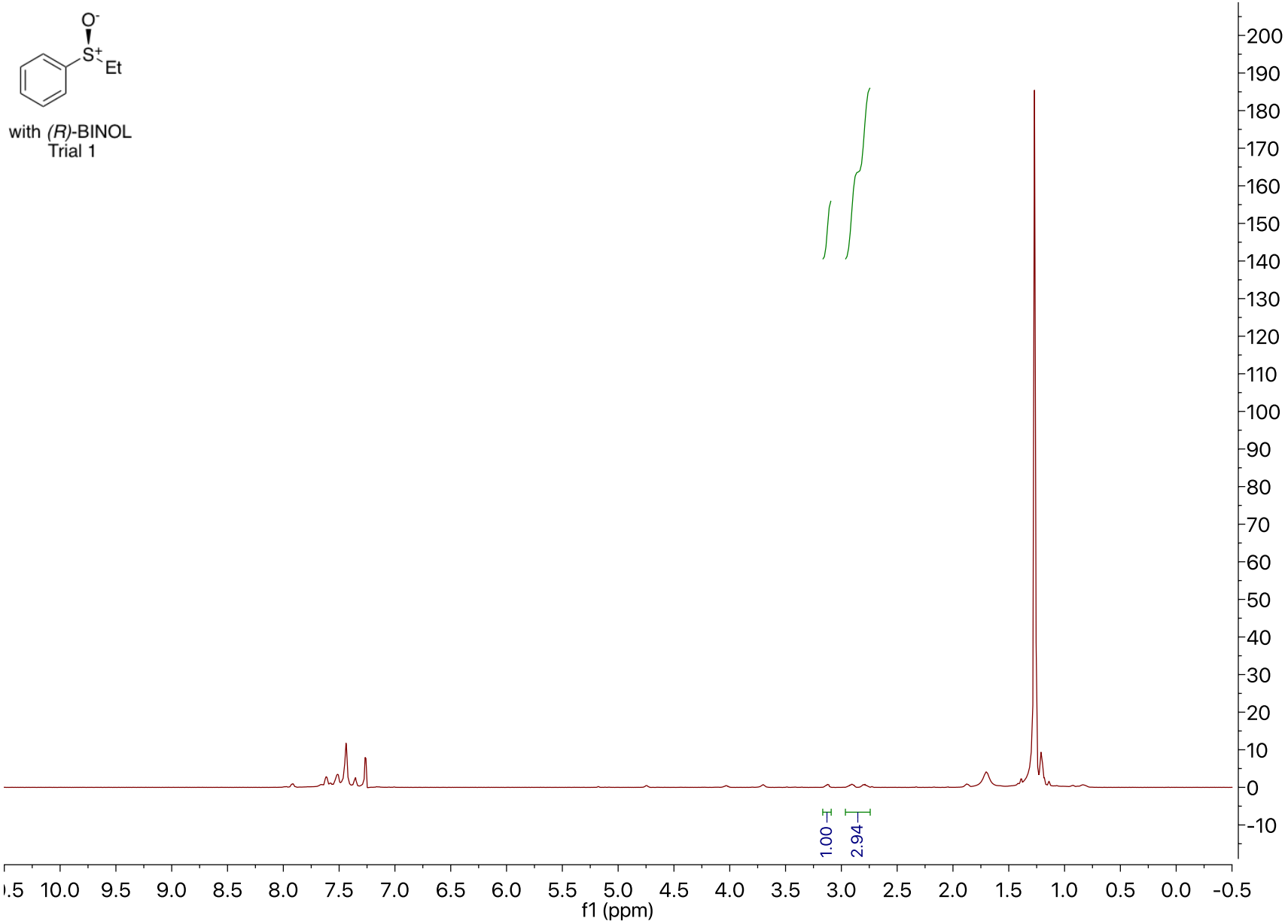
Appendix A:

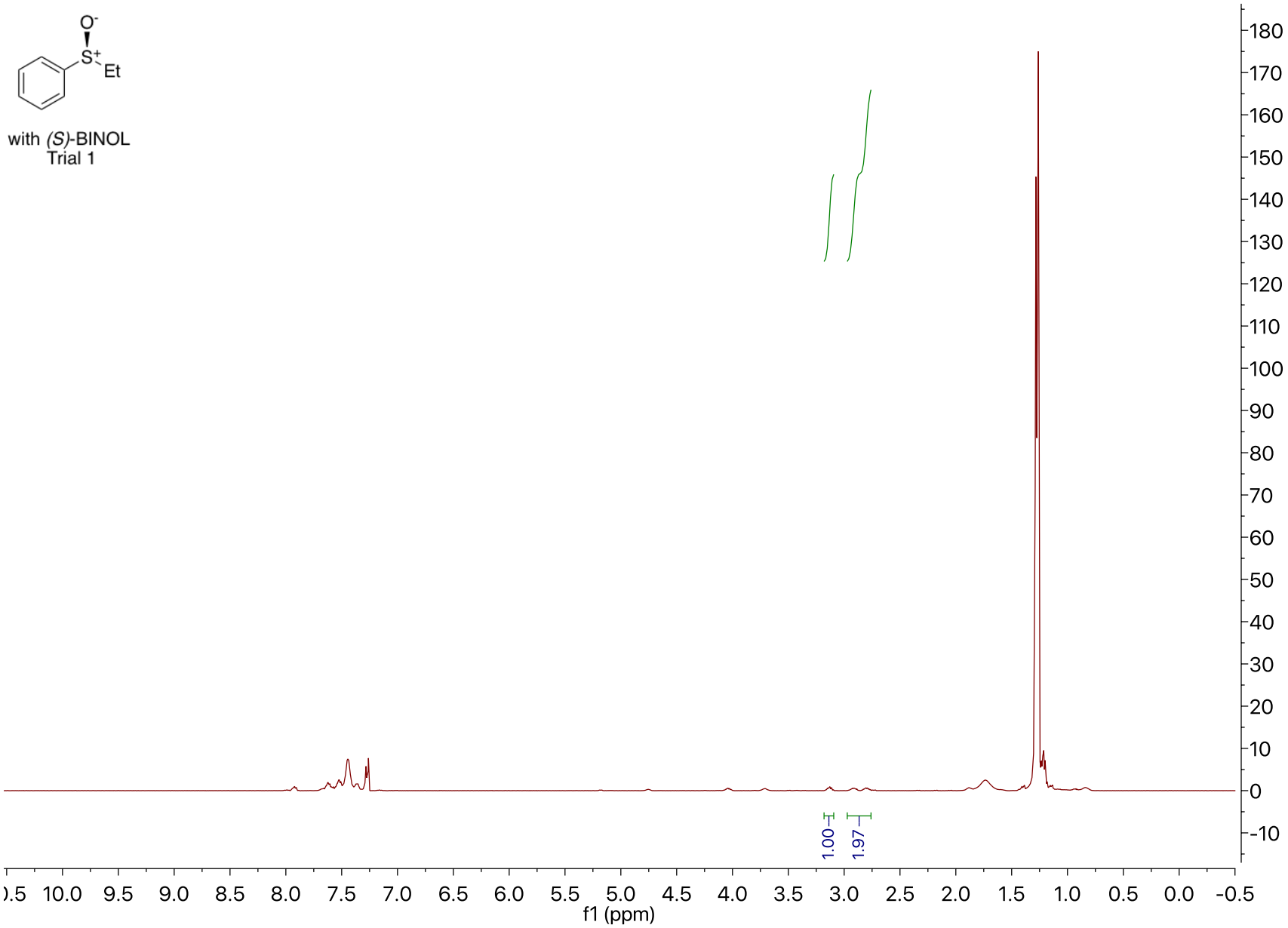
NMR Spectra of CEC Experiments for Chapter 1

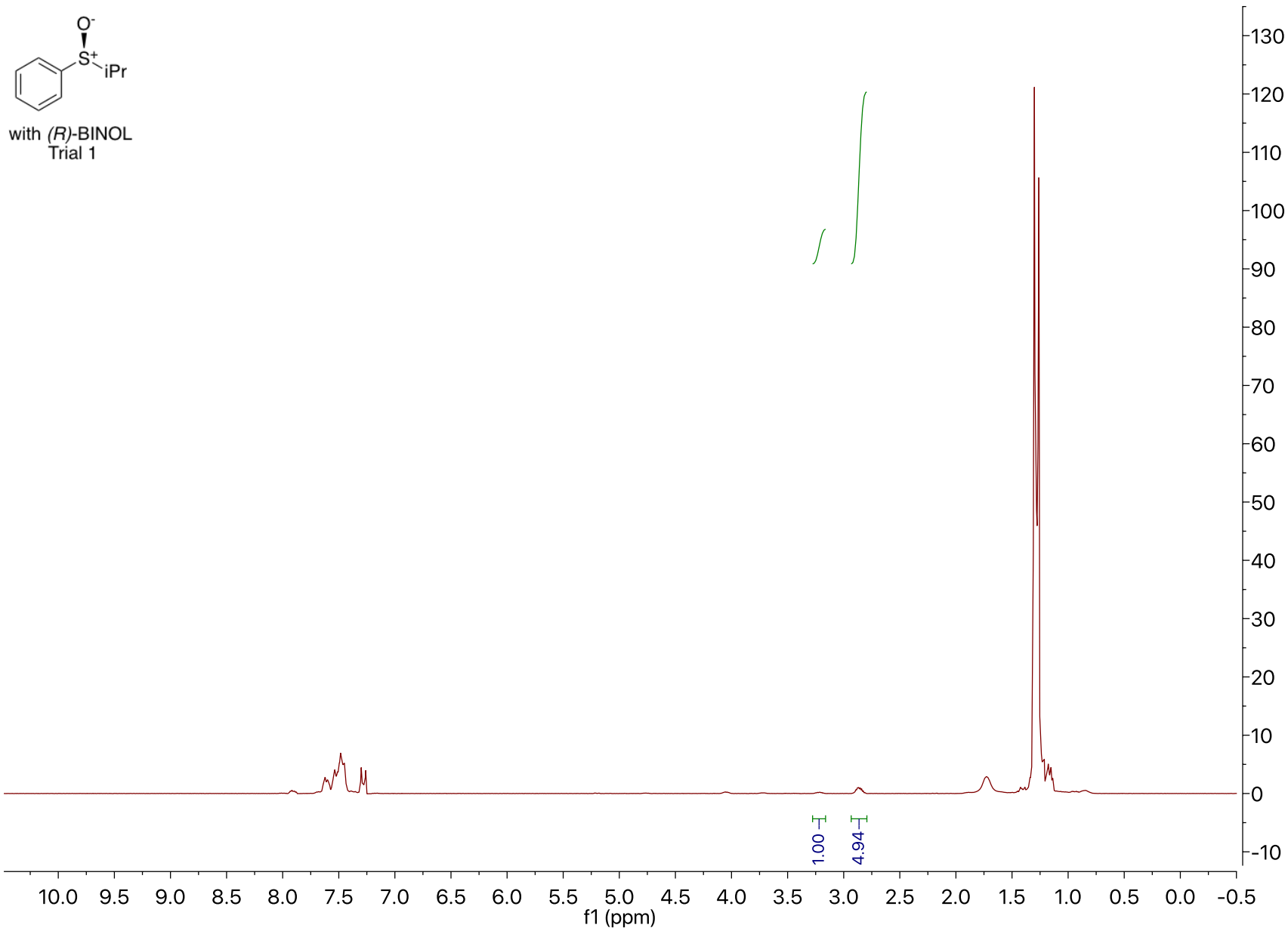


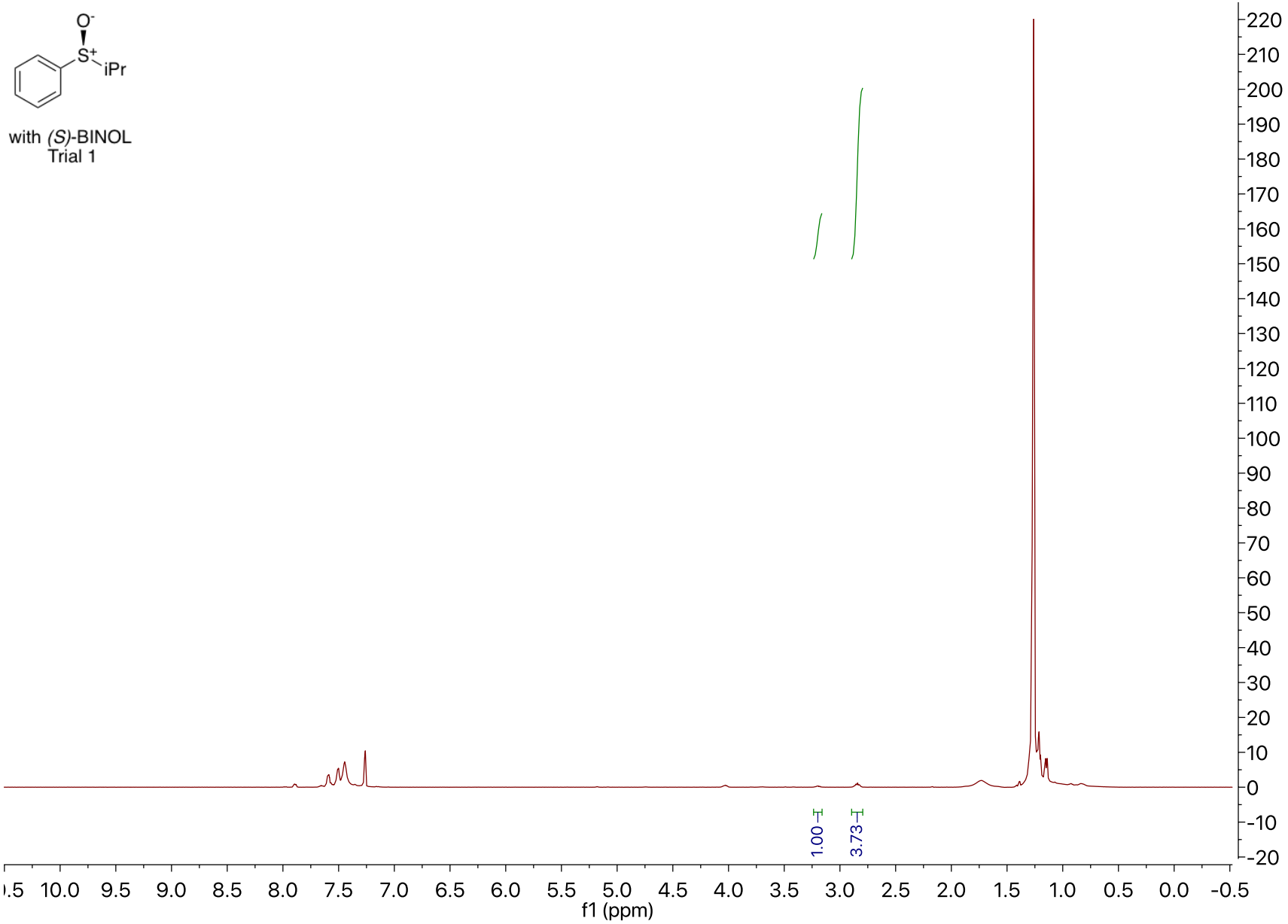
62

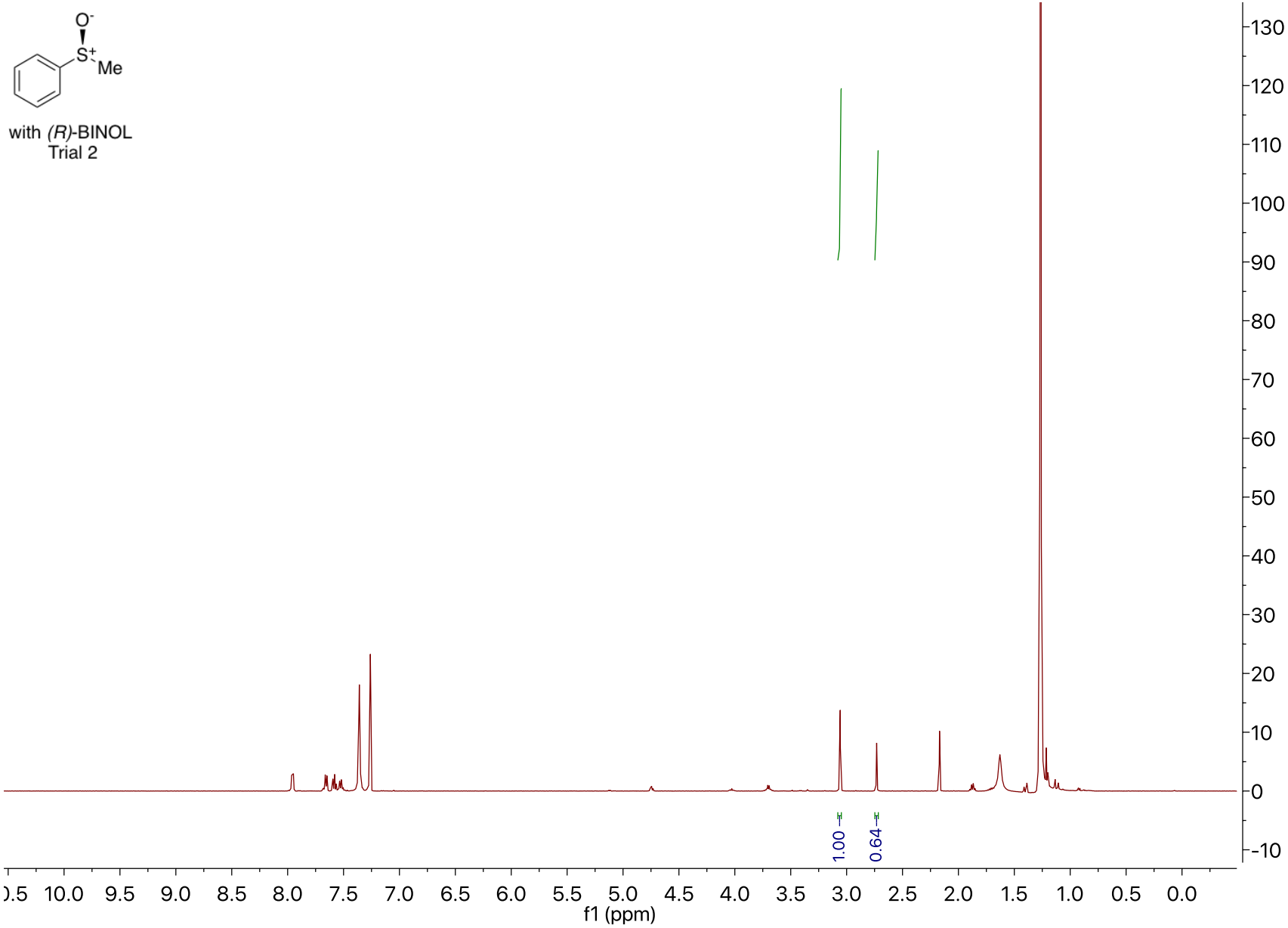

O⁻
S⁺
Me
with (S)-BINOL
Trial 1
1.00
1.91
f1 (ppm)

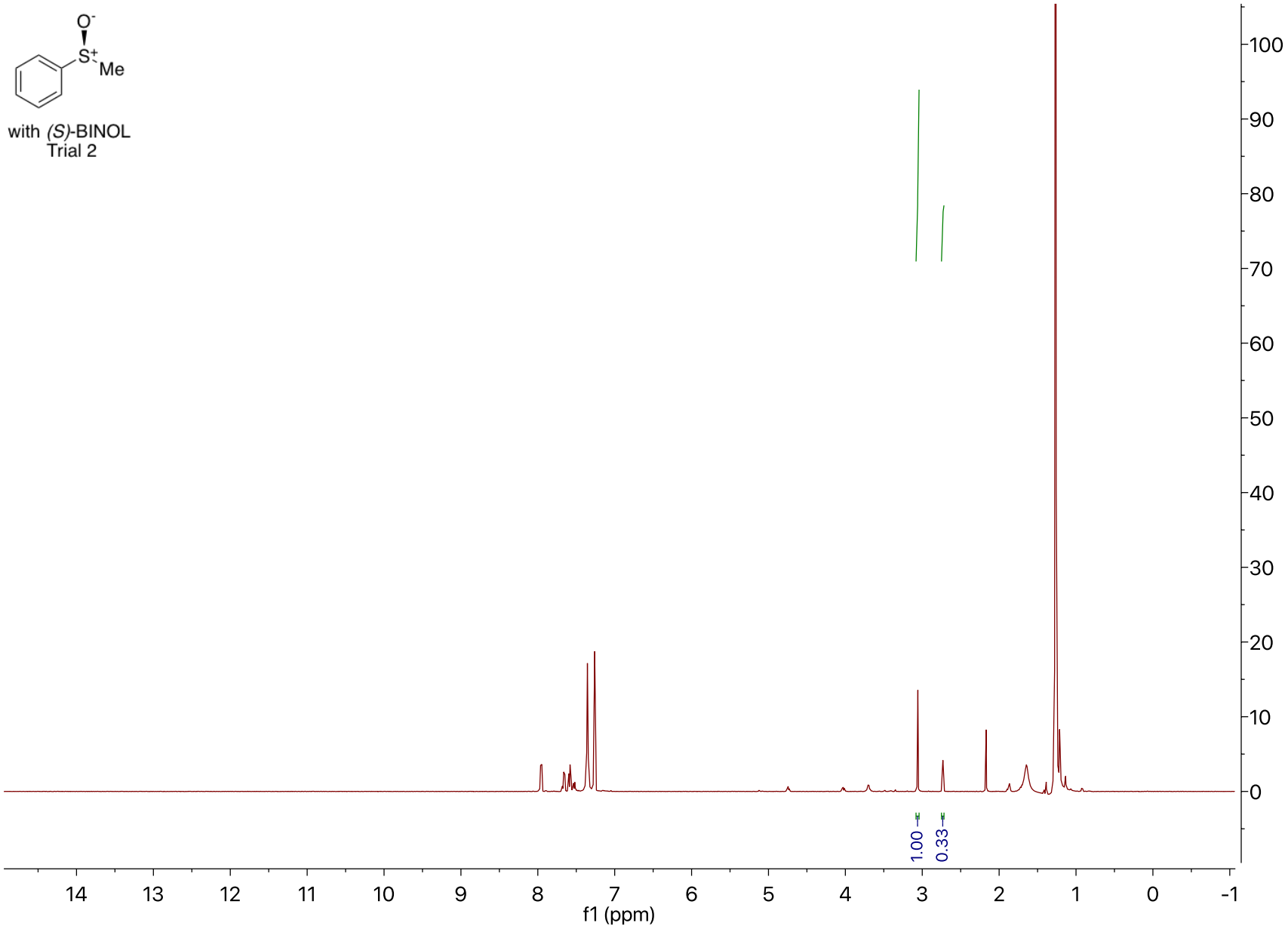

O-
S+
Et
with (R)-BINOL
Trial 1
1.00
2.94
f1 (ppm)

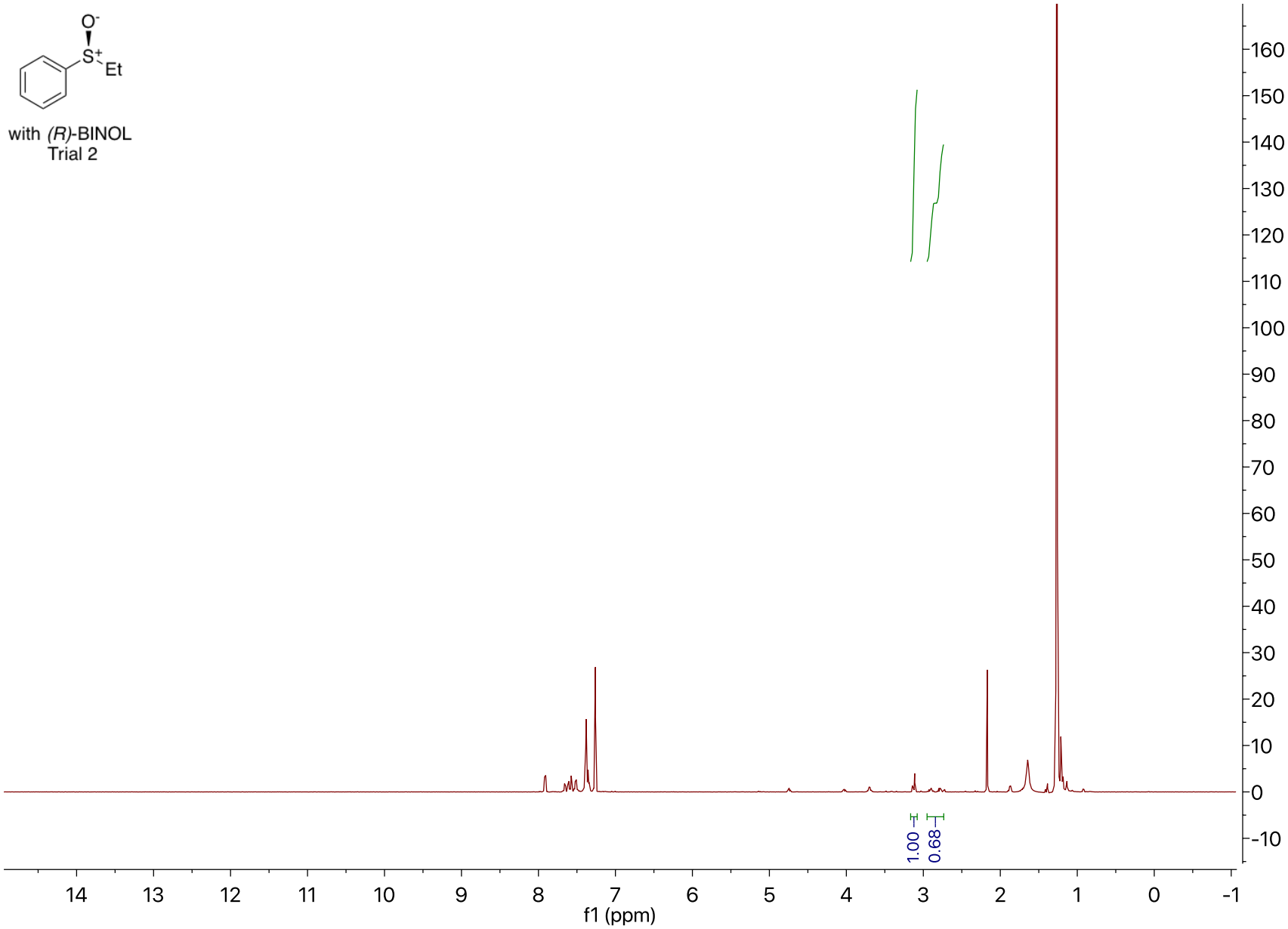

O
S+
Et
with (S)-BINOL
Trial 1
1.00
1.97
f1 (ppm)

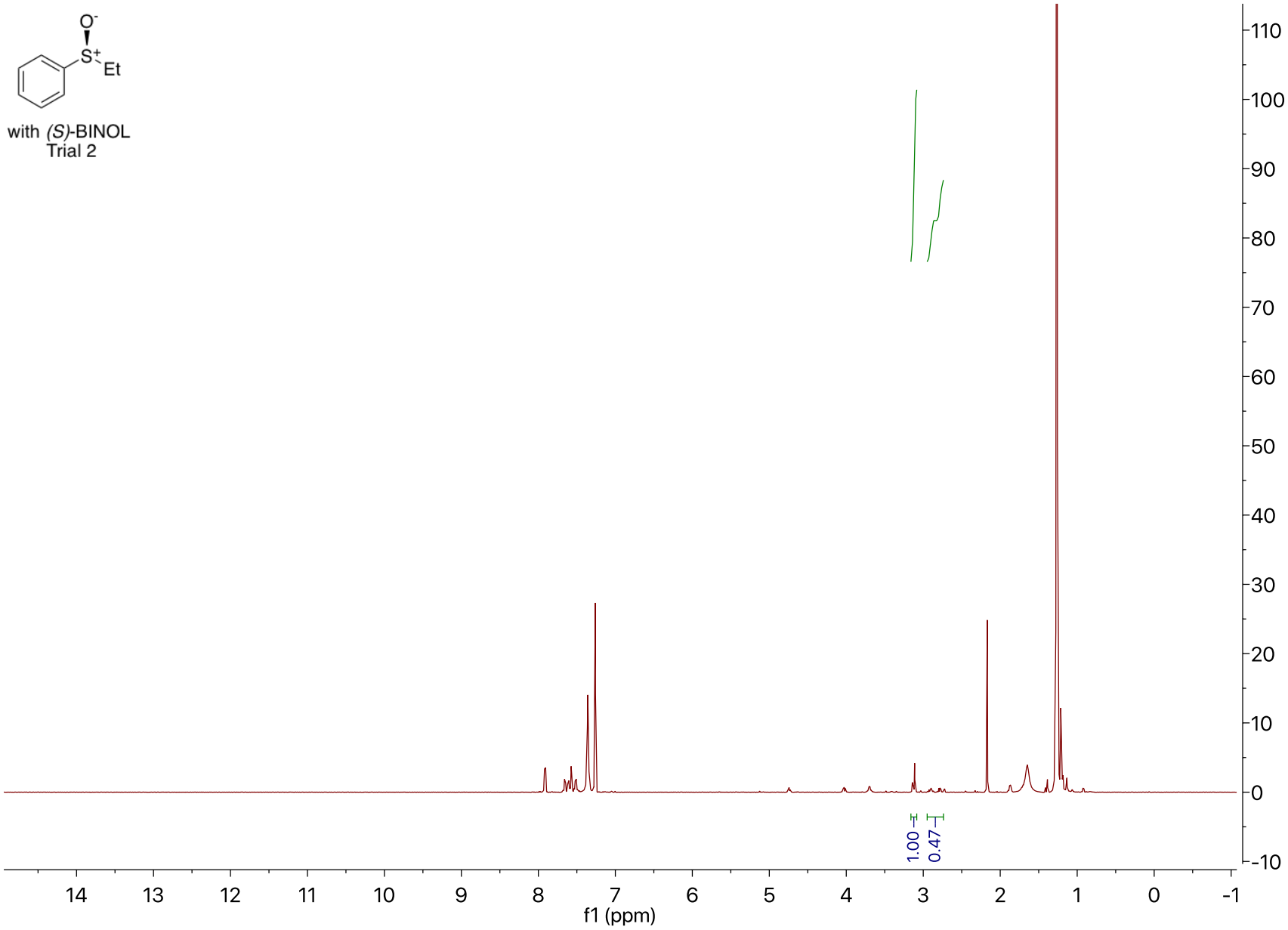

O⁻
S⁺
iPr
with (R)-BINOL
Trial 1
99
1.00
4.94
f1 (ppm)

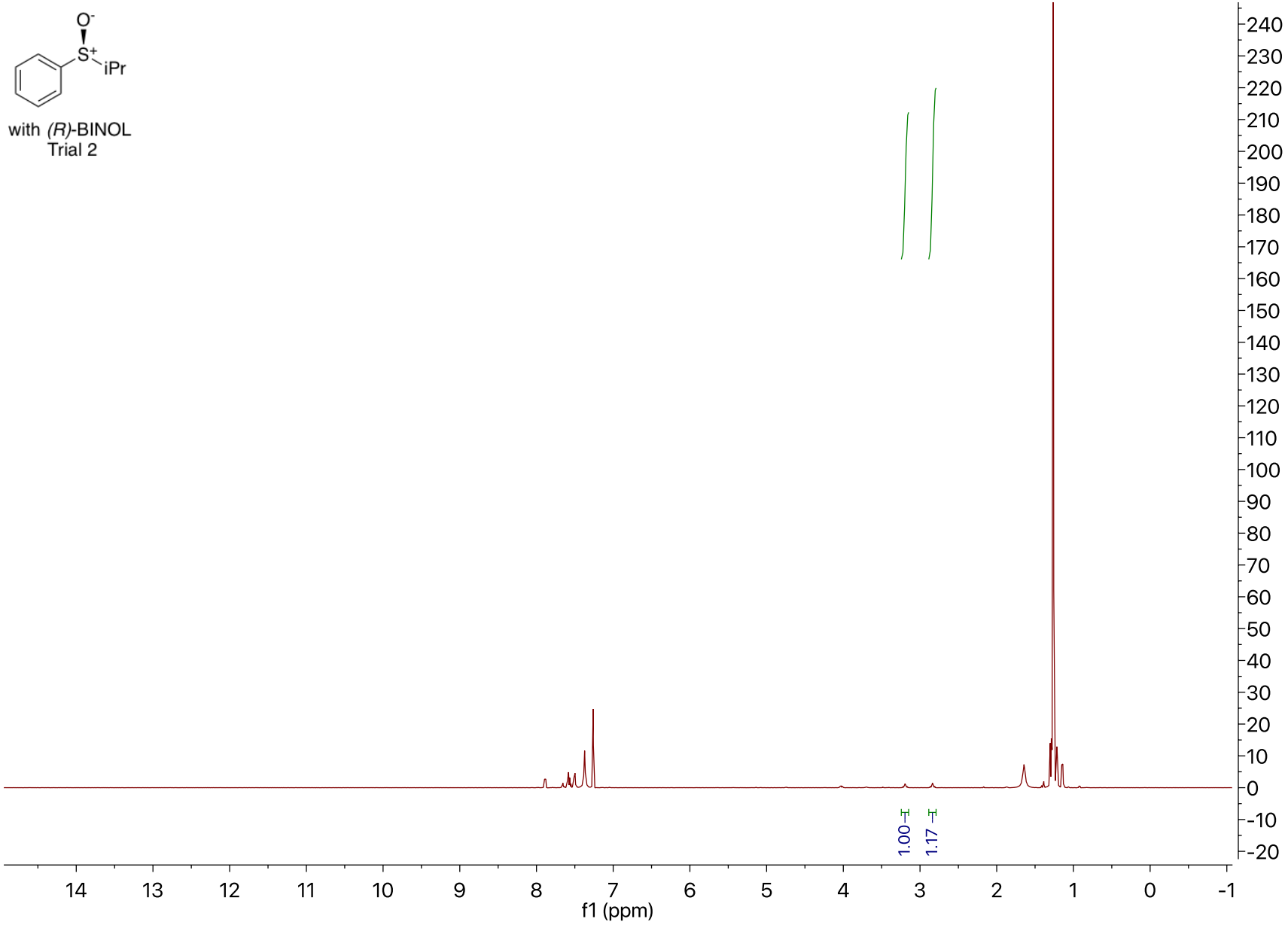

O-
S+
iPr
with (S)-BINOL
Trial 1
1.00
3.73
f1 (ppm)

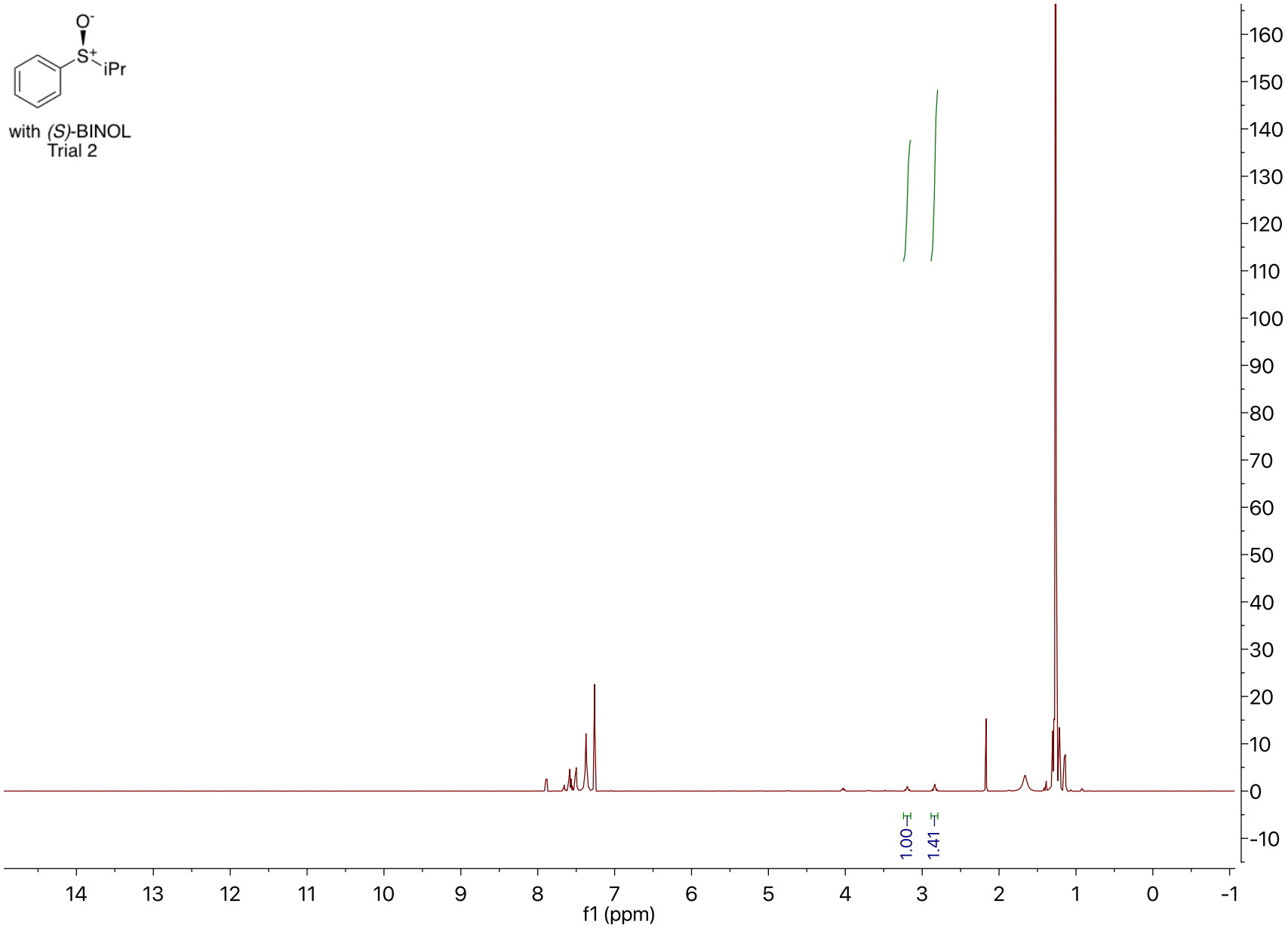

O⁻
S⁺
Me
with (R)-BINOL
Trial 2
1.00
0.64
f1 (ppm)

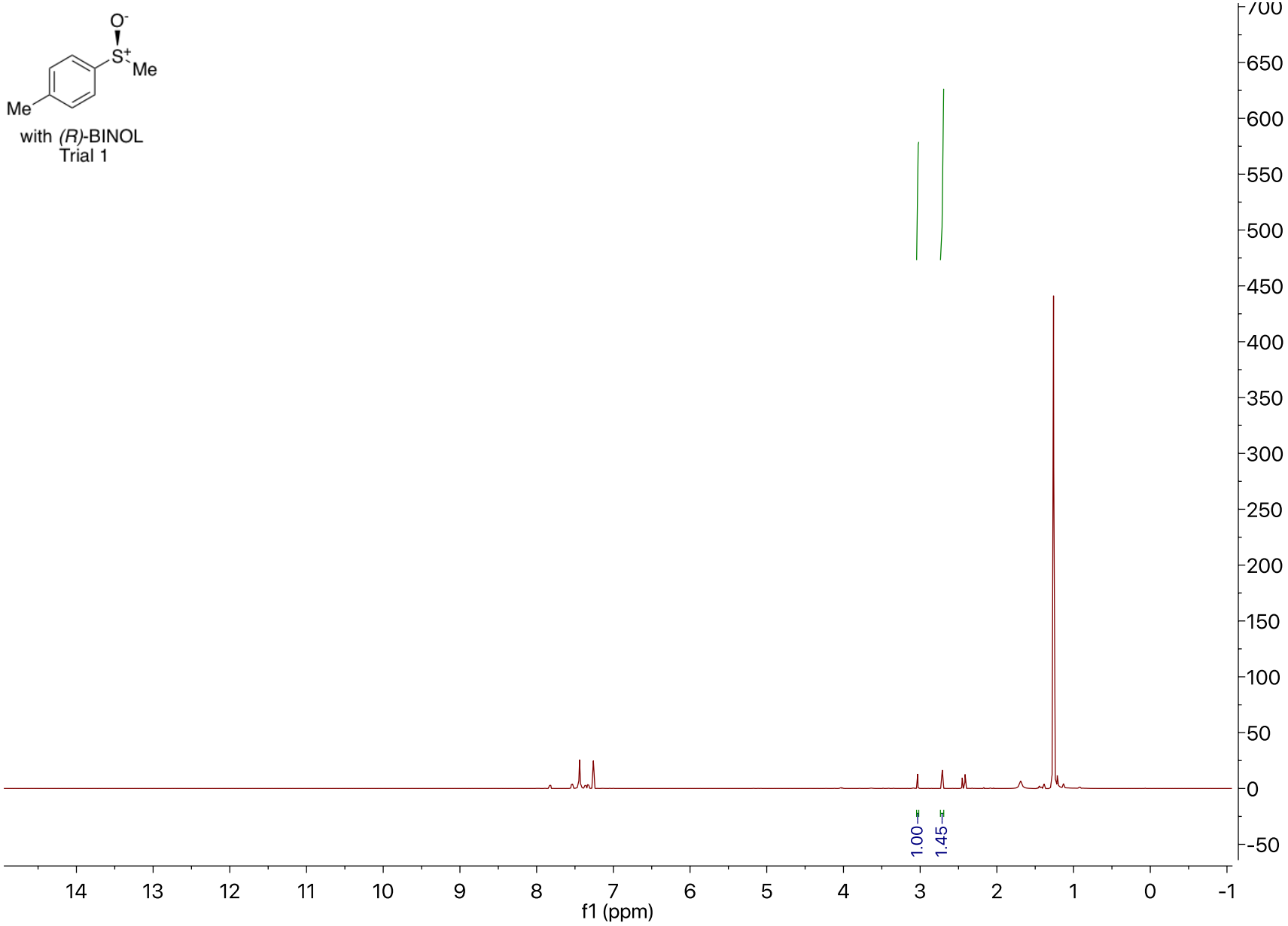

O
S
Me
with (S)-BINOL
Trial 2
69
100
90
80
70
60
50
40
30
20
10
0
1.00
0.33
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

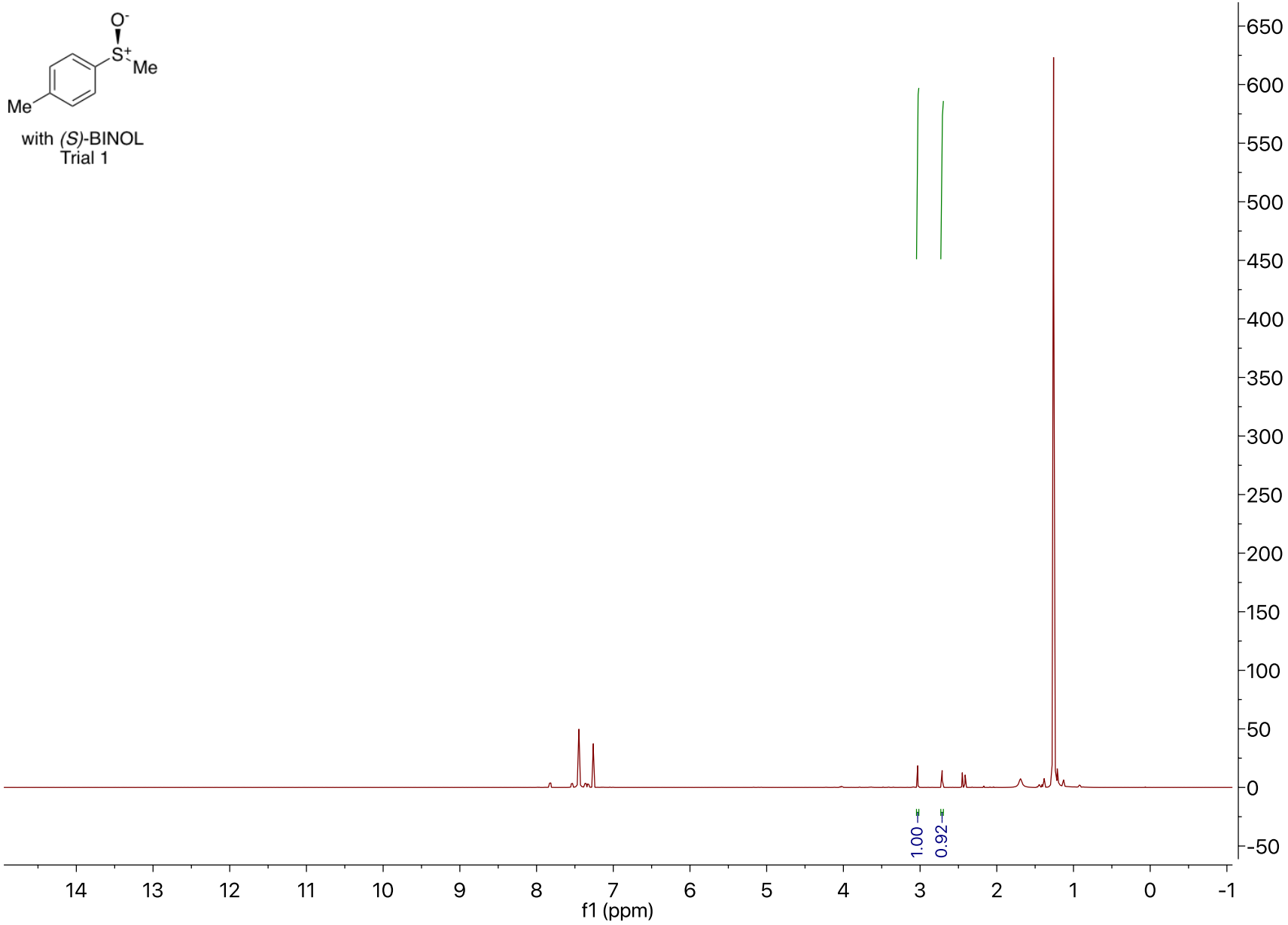

O
S+
Et
with (R)-BINOL
Trial 2
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
1.00
0.68
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

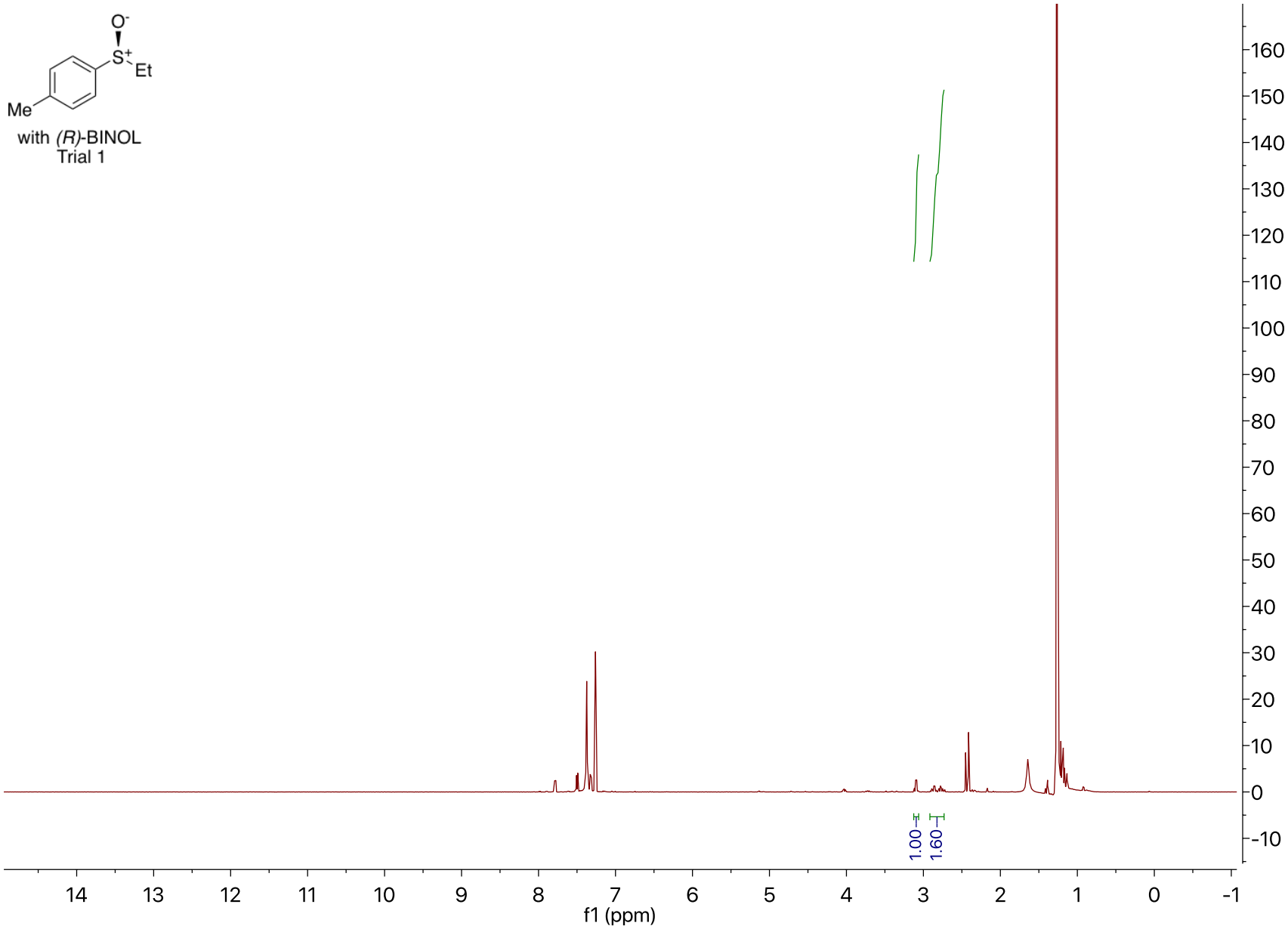

with (S)-BINOL
Trial 2
1.00
0.47
f1 (ppm)

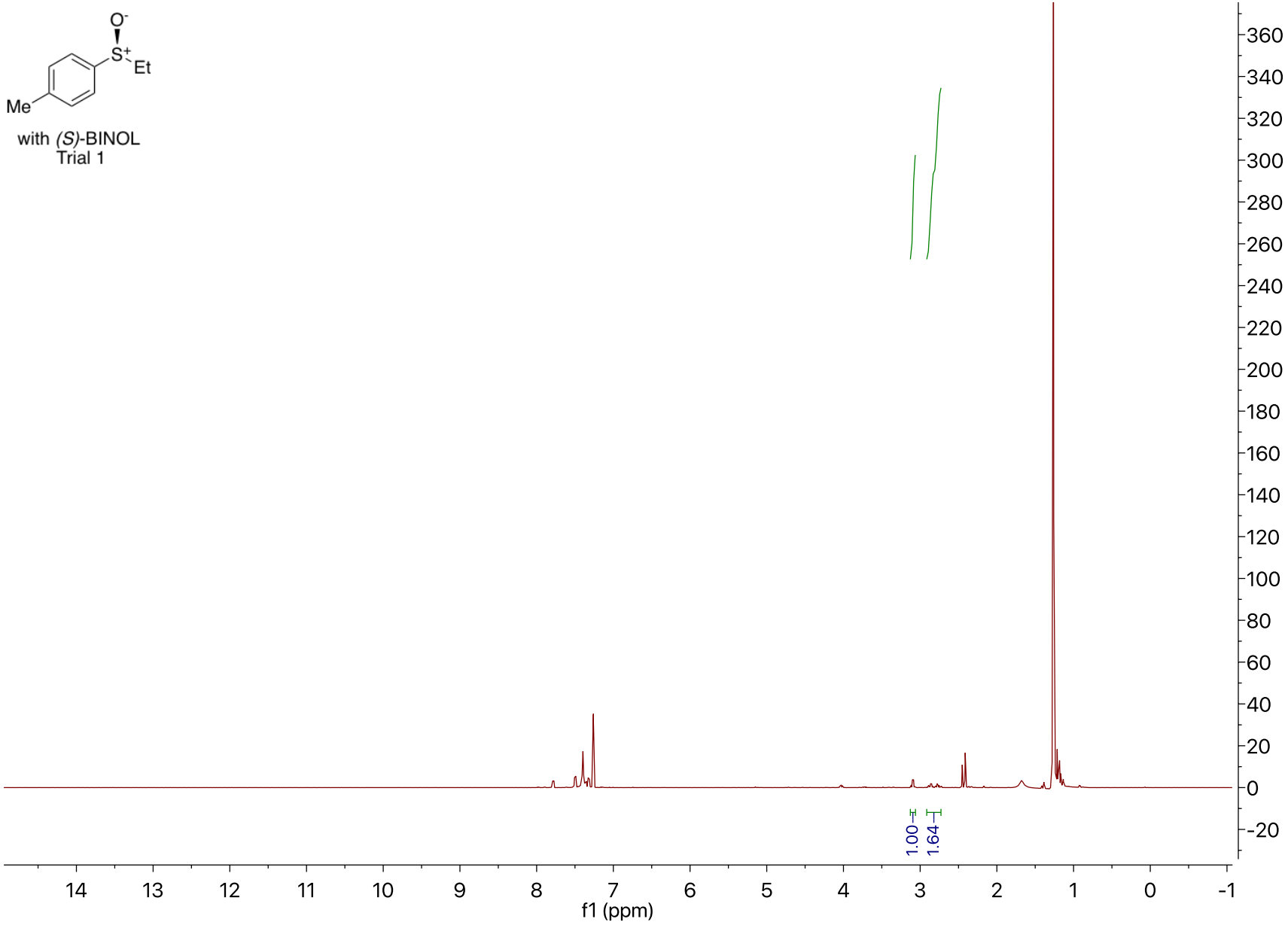

O⁻
S⁺
iPr
with (R)-BINOL
Trial 2
1.00
1.17
f1 (ppm)

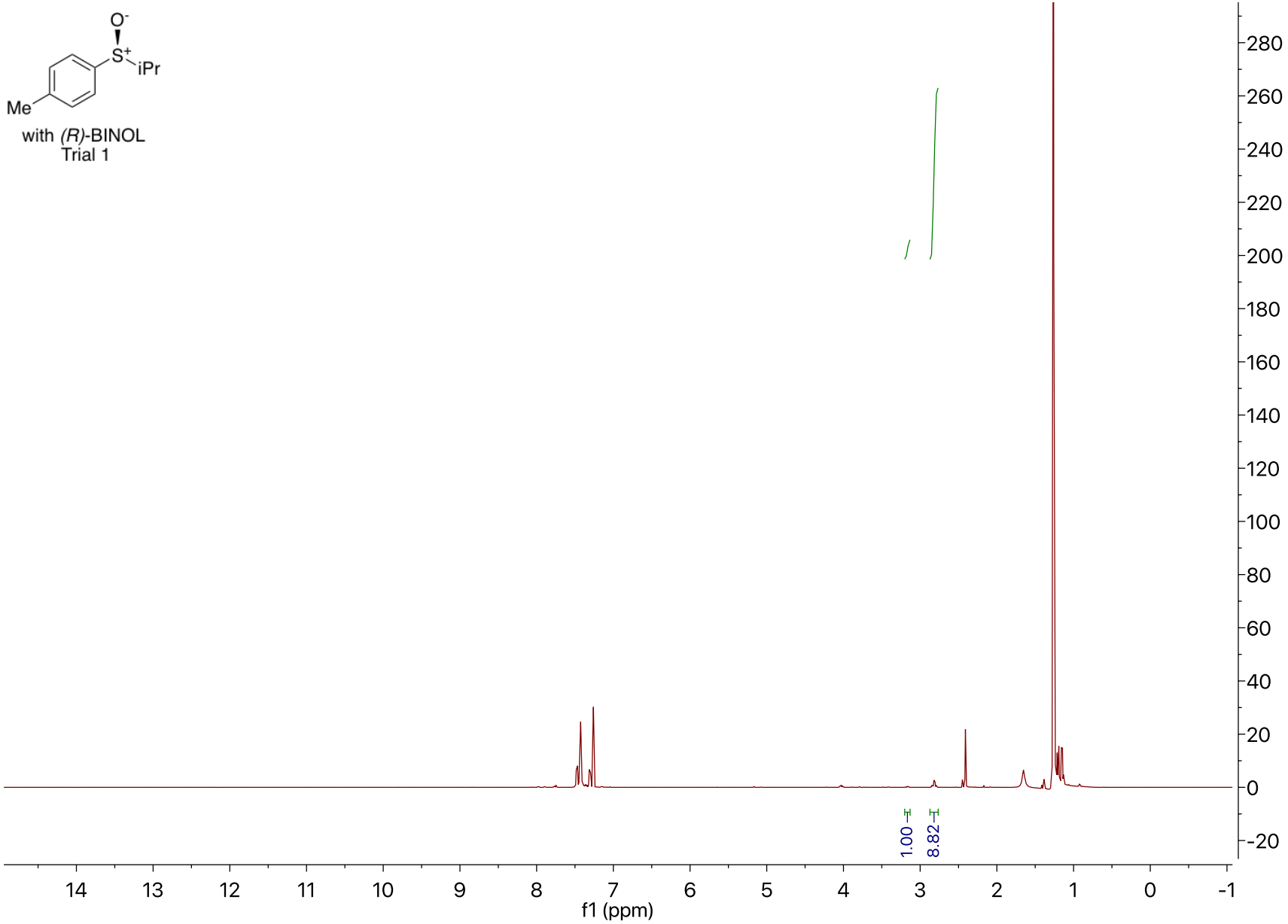

O-
S+
iPr
with (S)-BINOL
Trial 2
1.00
1.41
f1 (ppm)

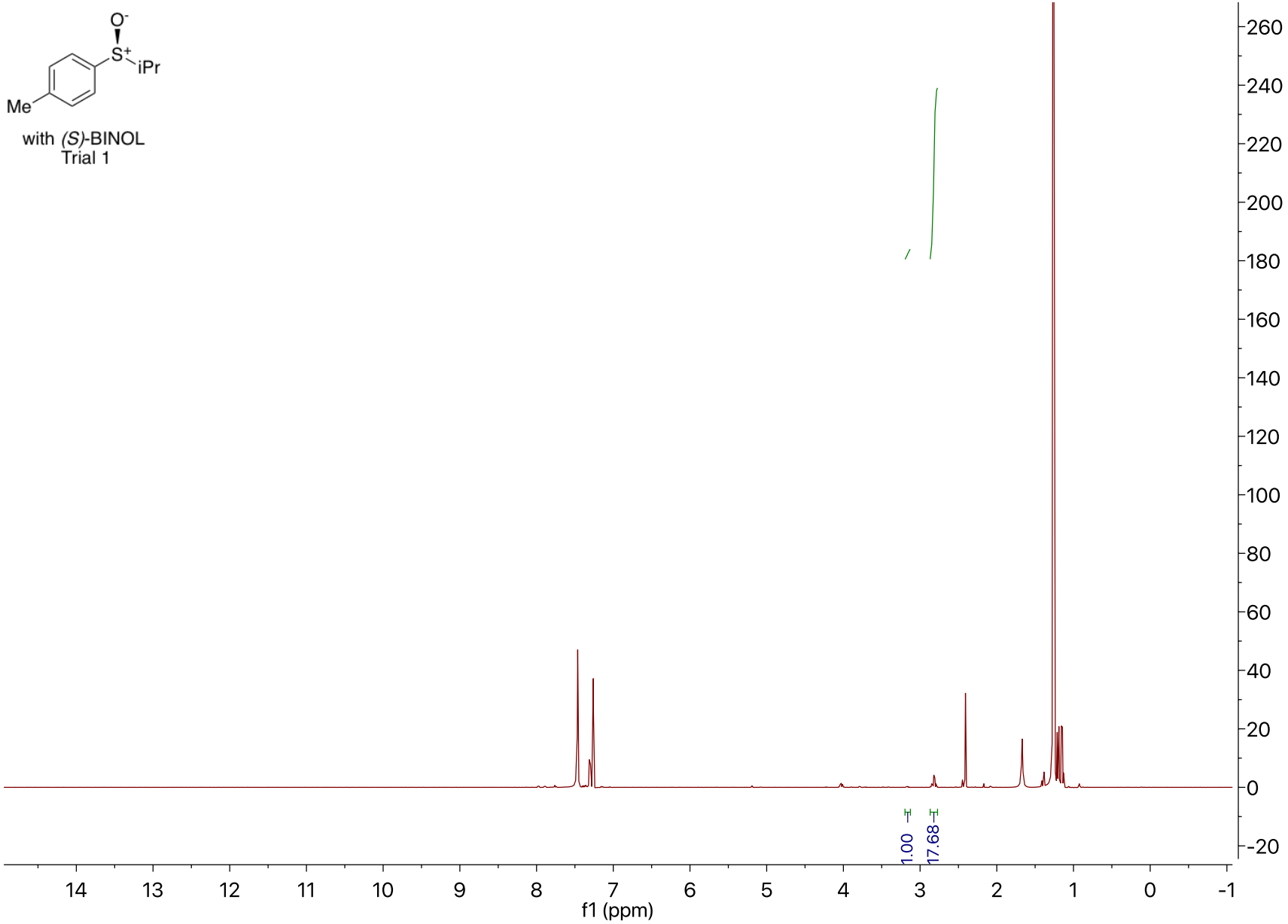

O⁻
S⁺
Me
Me
with (R)-BINOL
Trial 1
1.00
1.45
f1 (ppm)

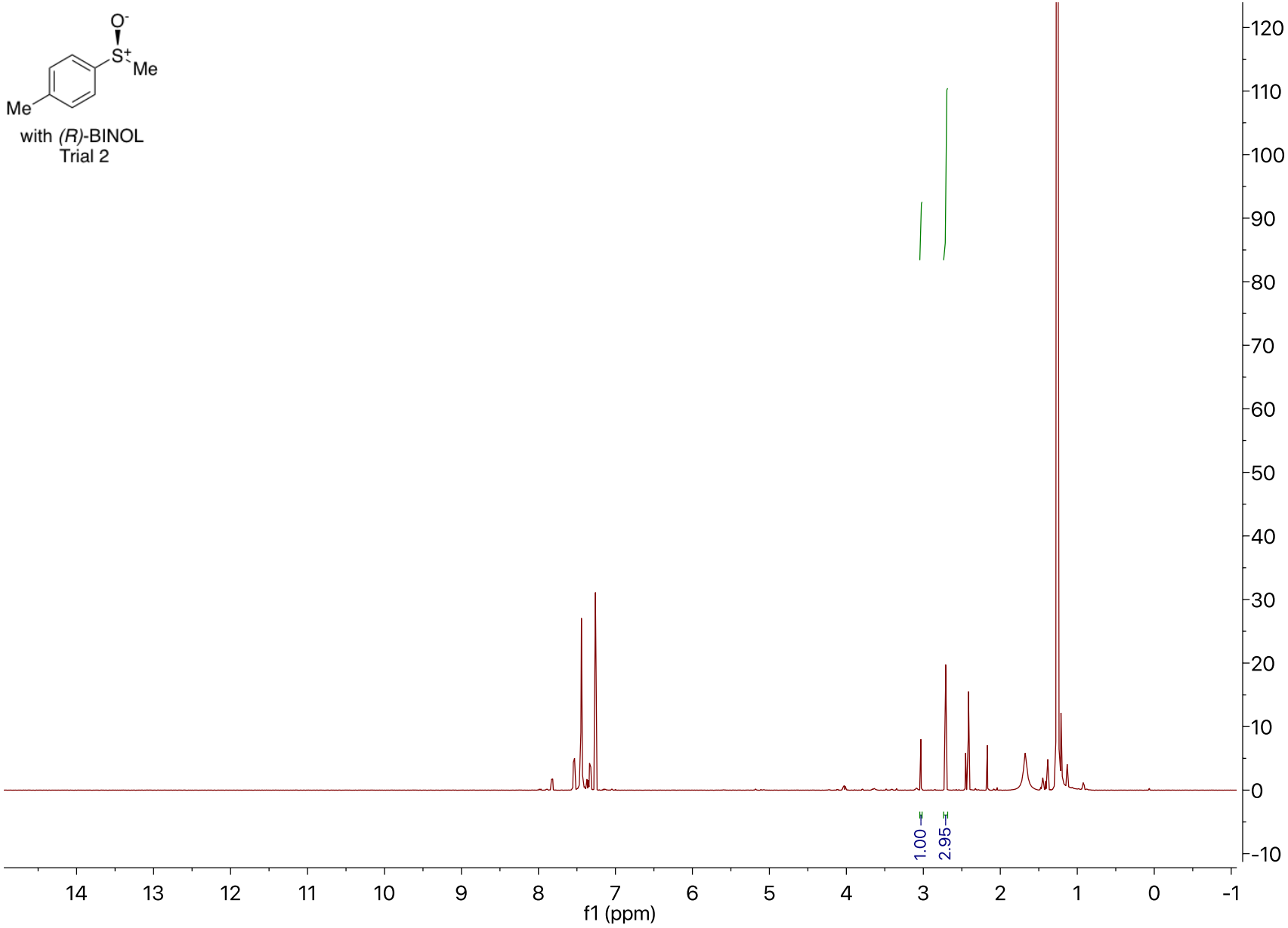

O-
S+
Me
Me
with (S)-BINOL
Trial 1
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
1.00
0.92
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

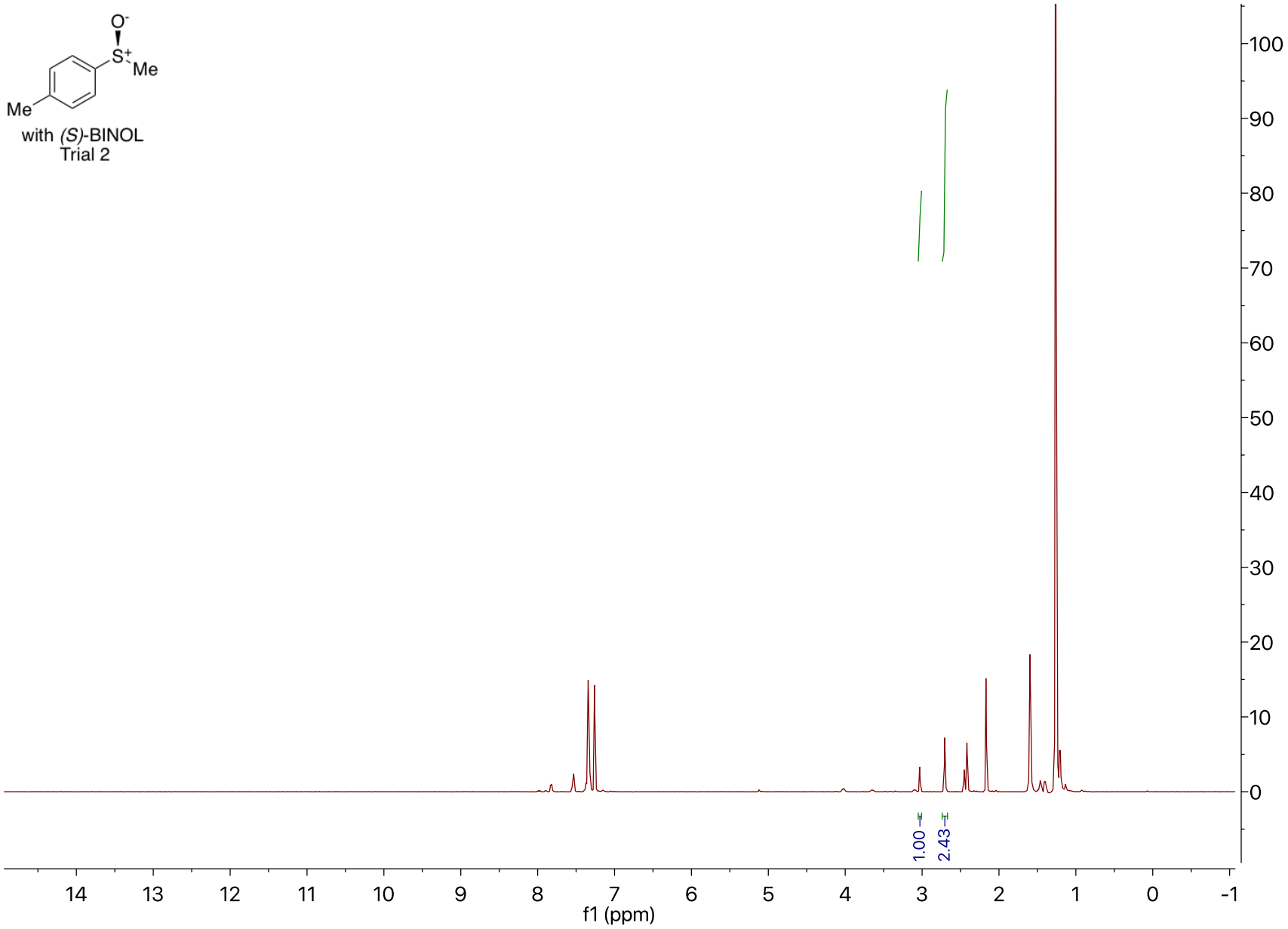

O
S+
Et
Me
with (R)-BINOL
Trial 1
1.00
1.60
f1 (ppm)

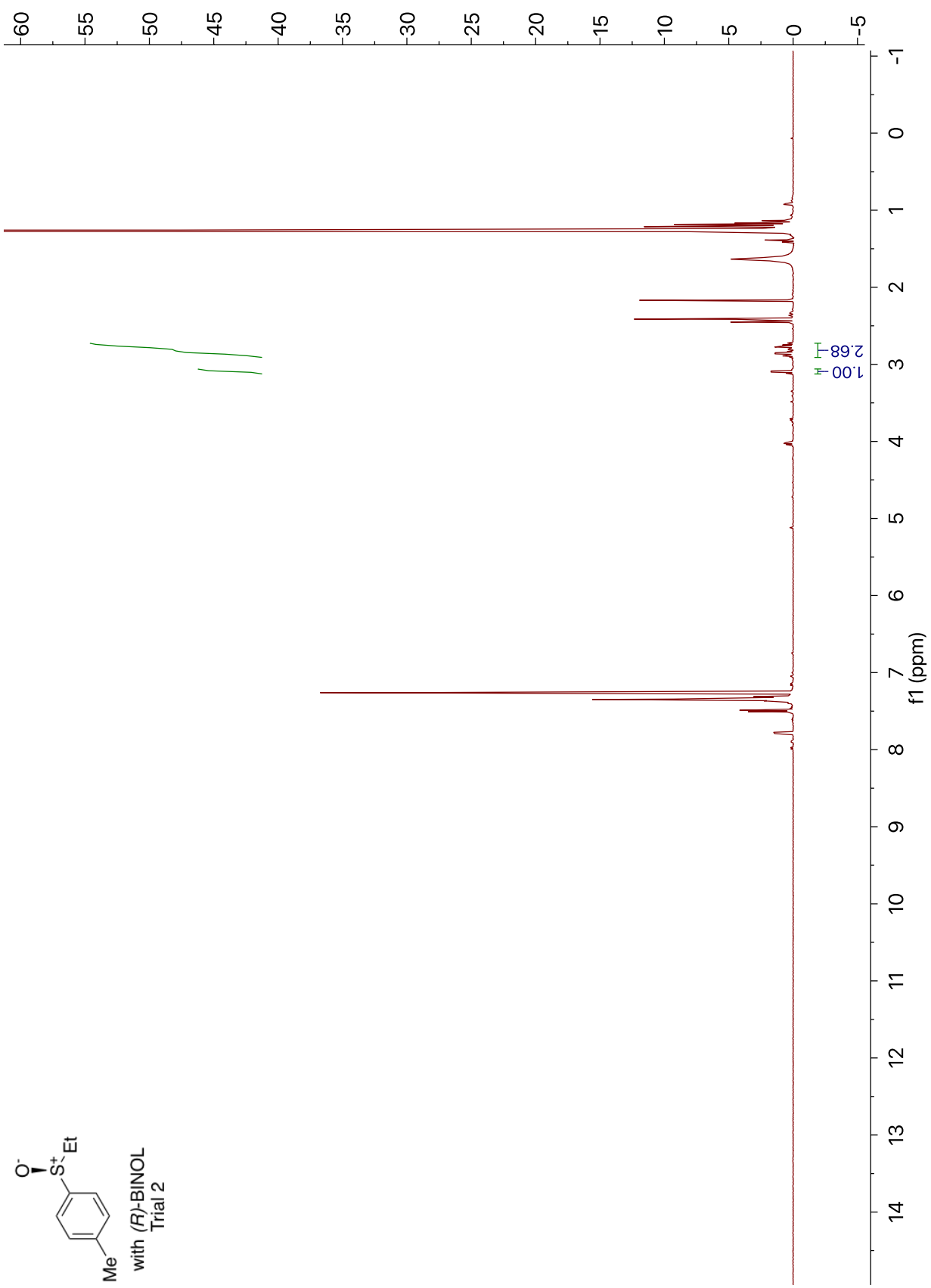

O⁻
S⁺
Et
Me
with (S)-BINOL
Trial 1
1.00
1.64
f1 (ppm)

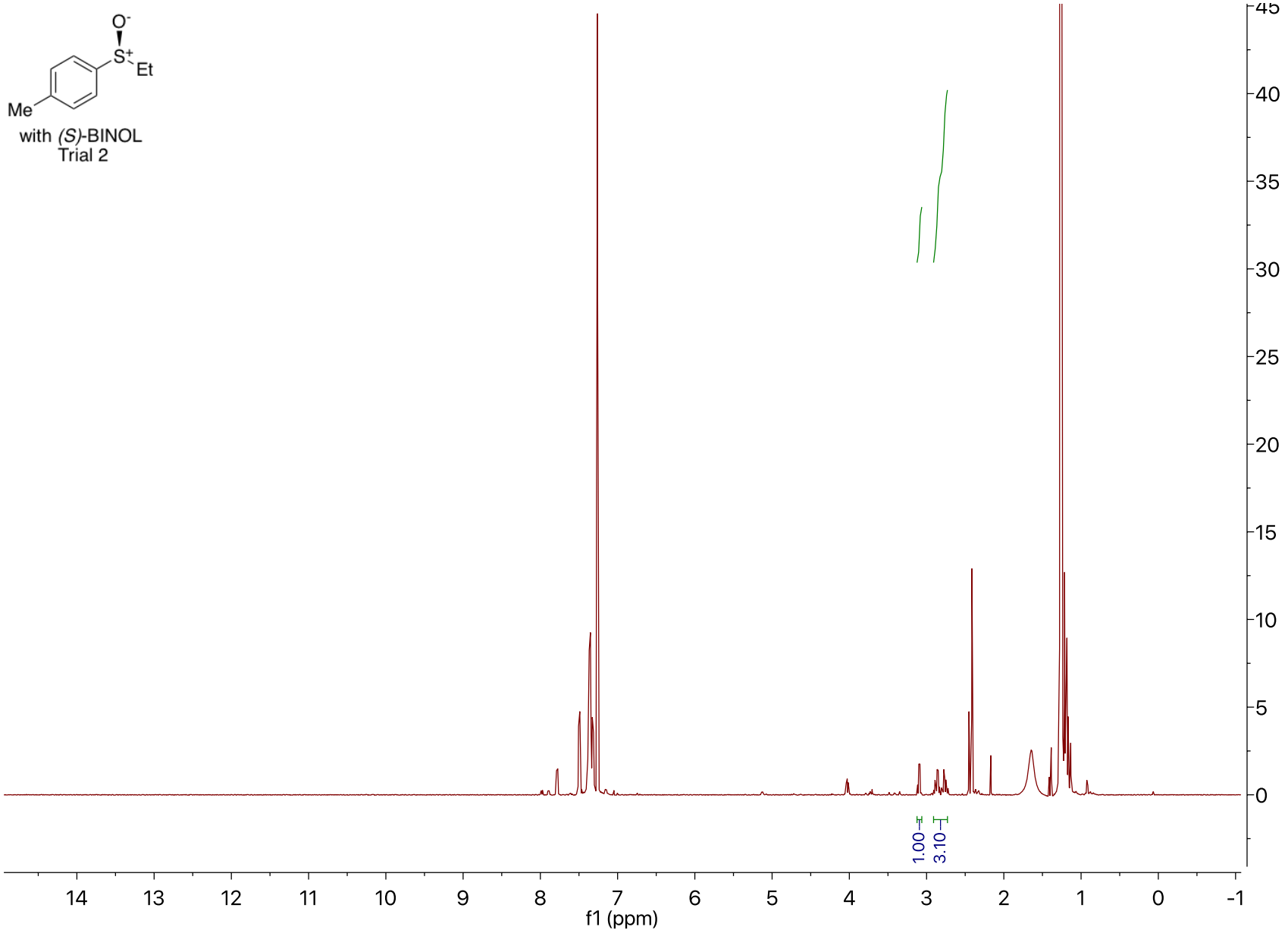

O⁻
S⁺
iPr
Me
with (R)-BINOL
Trial 1
1.00
8.82
f1 (ppm)

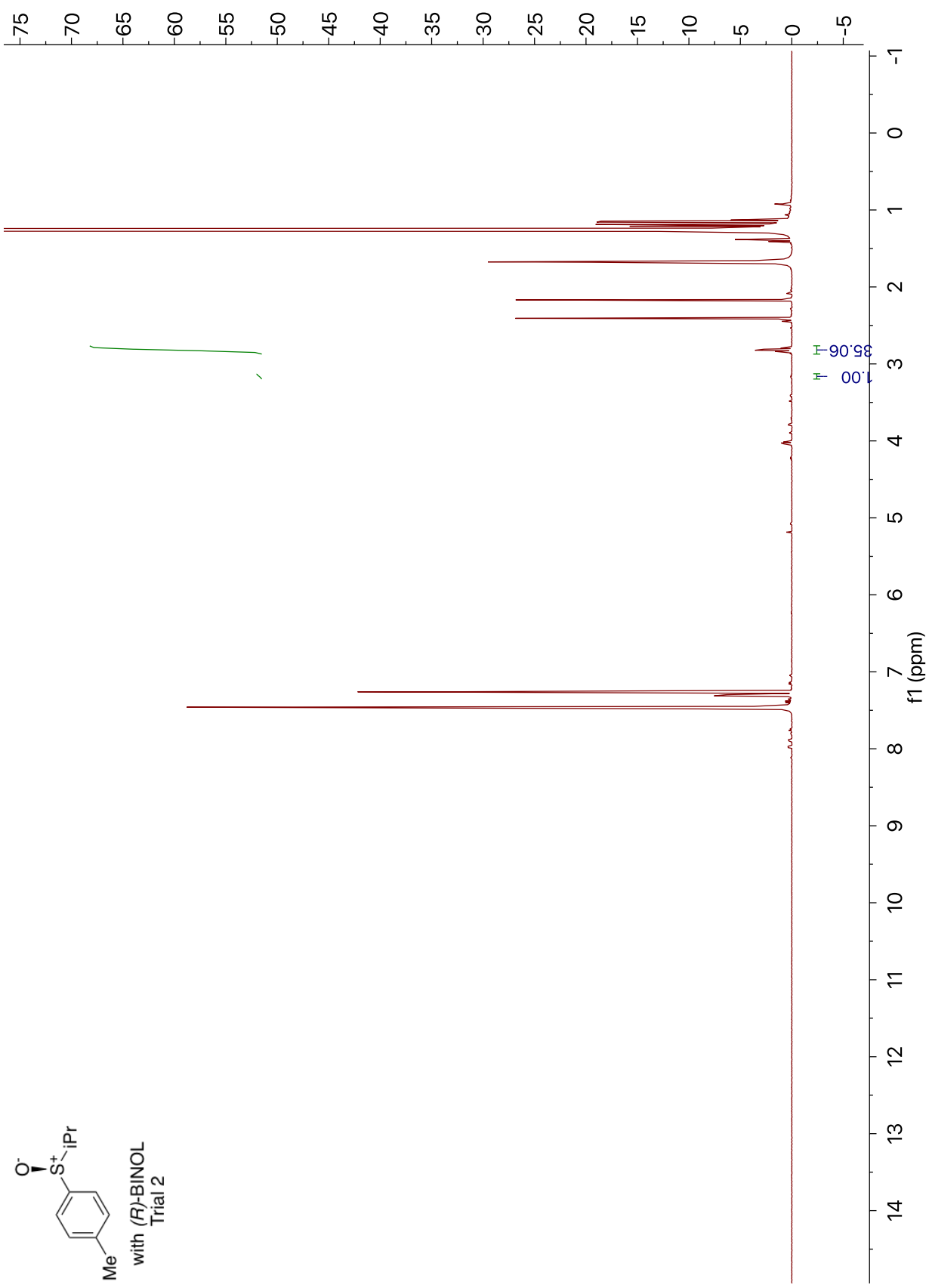

O
S+
iPr
Me
with (S)-BINOL
Trial 1
1.00
17.68
f1 (ppm)

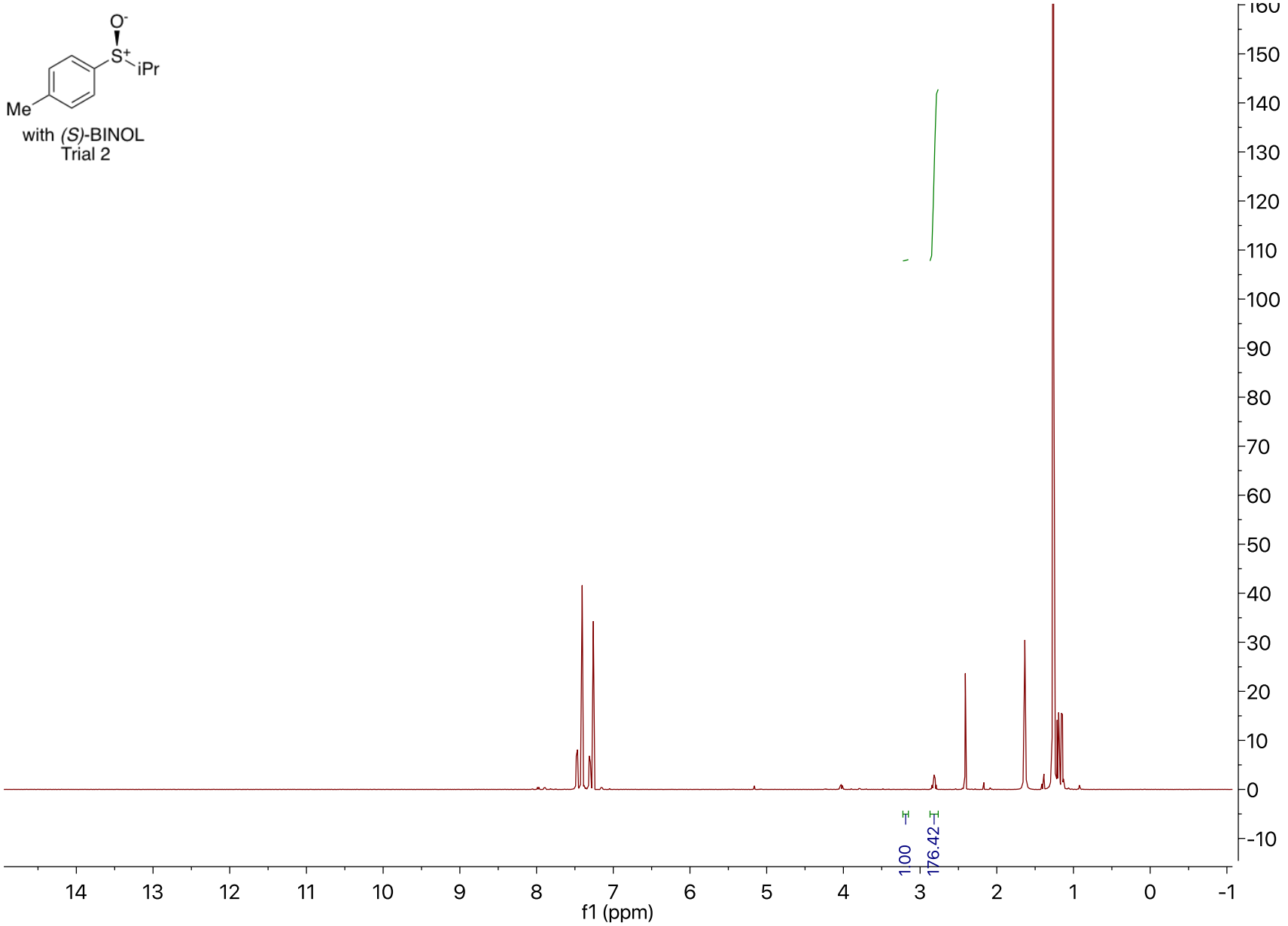

O
S+
Me
Me
with (R)-BINOL
Trial 2
1.00
2.95
f1 (ppm)

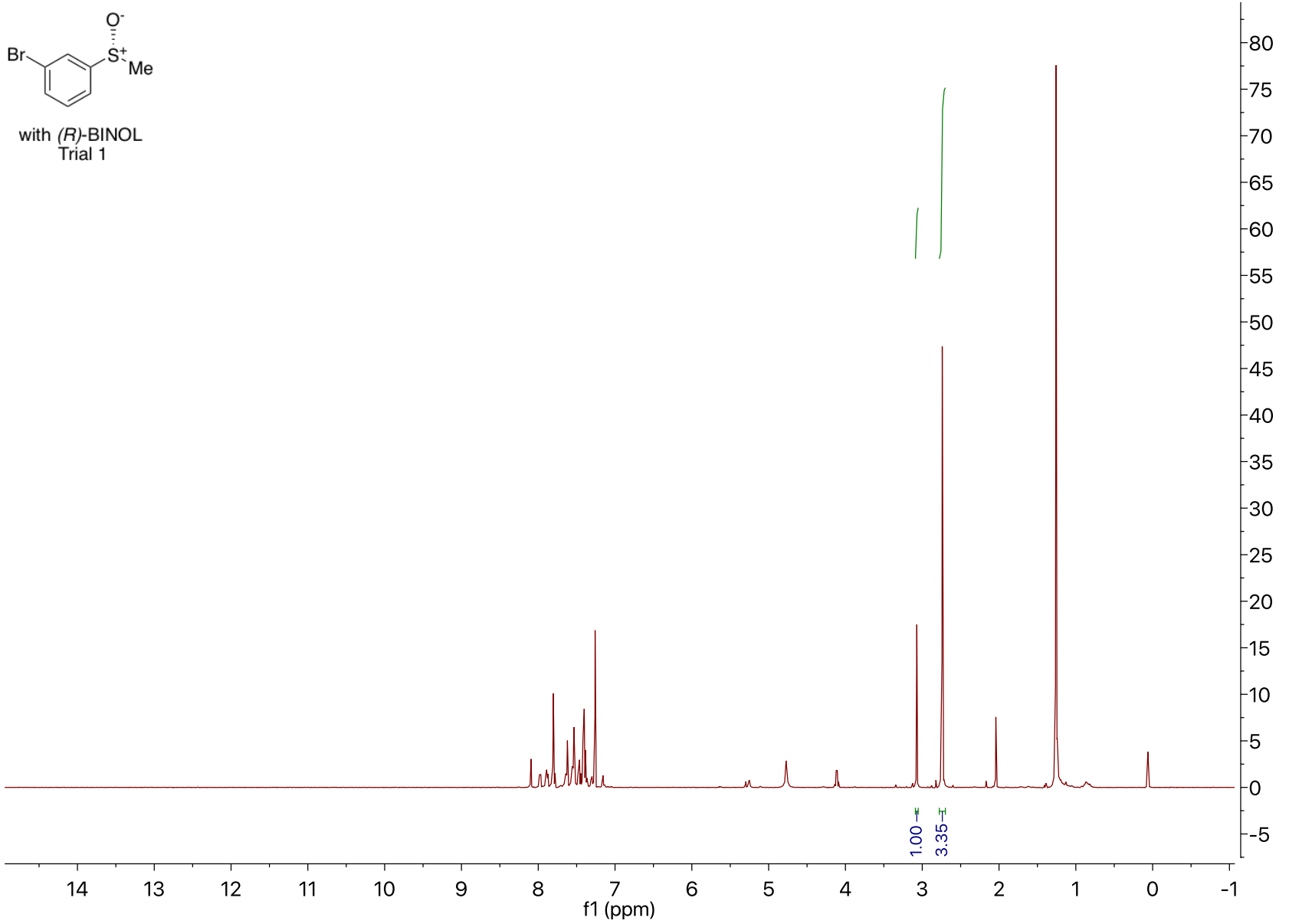

O
S+
Me
Me
with (S)-BINOL
Trial 2
1.00
2.43
f1 (ppm)

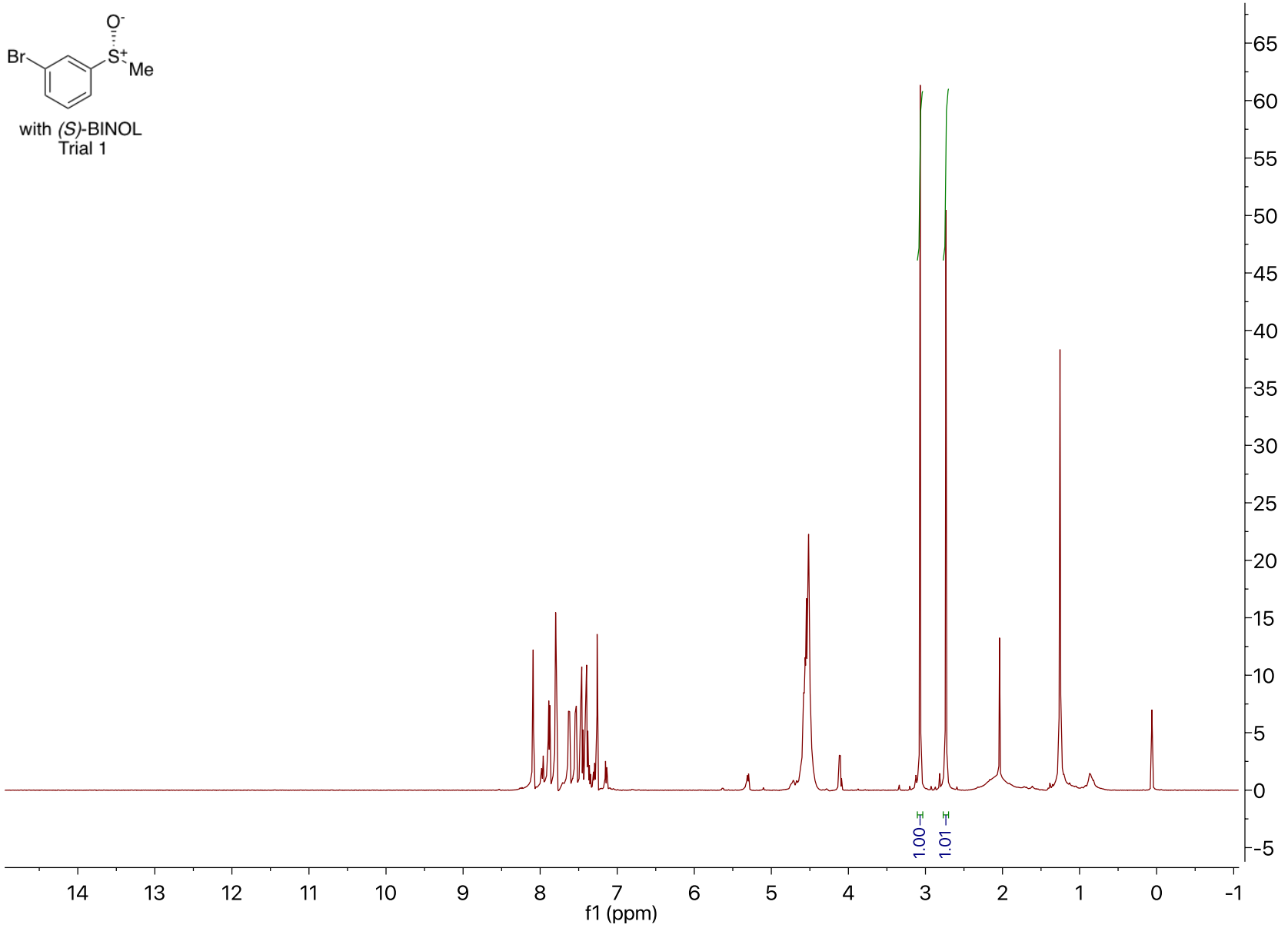

O
S+
Et
Me
with (R)-BINOL
Trial 2
2.68
1.00
f1 (ppm)

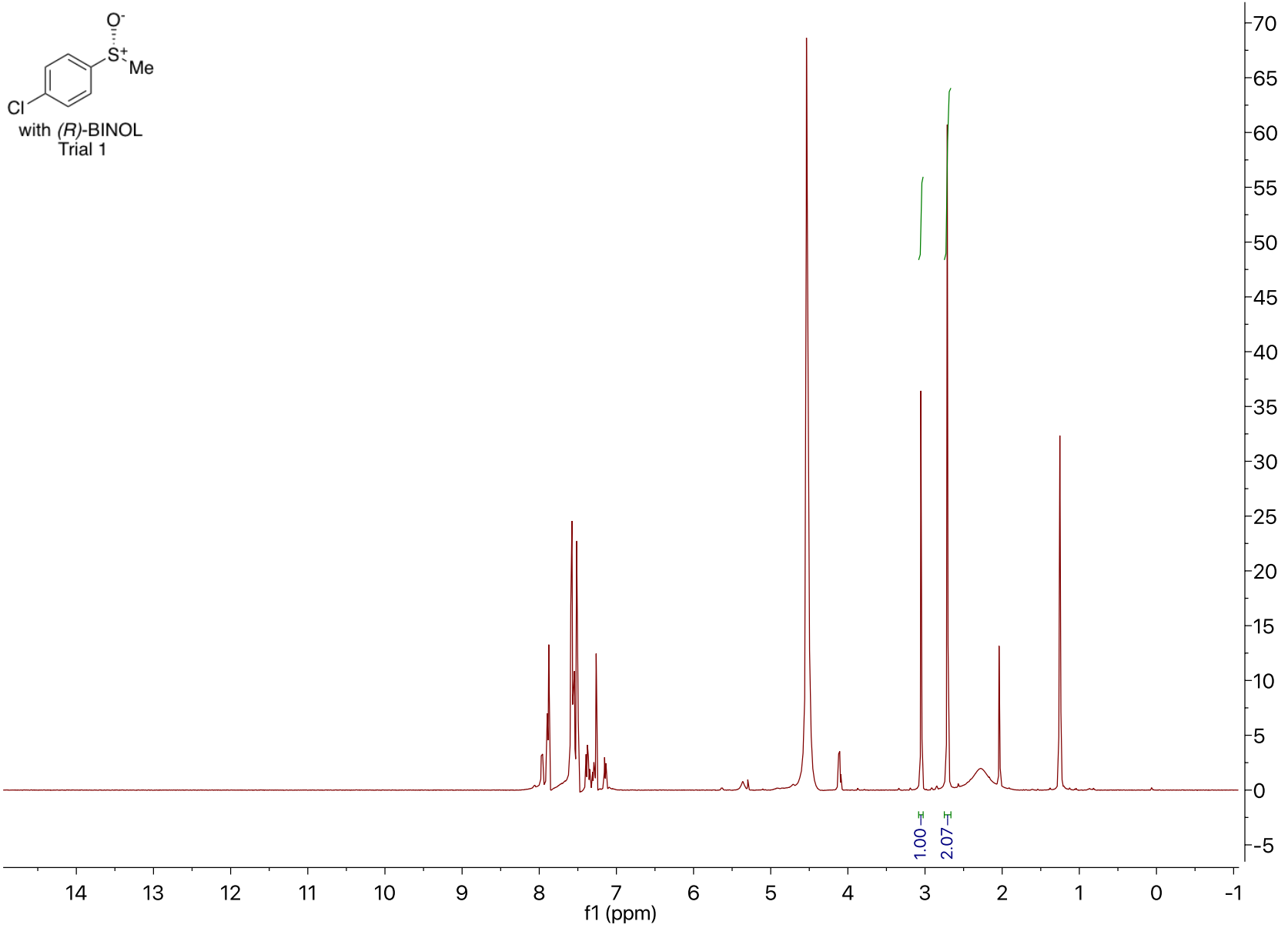

O
S+
Et
Me
with (S)-BINOL
Trial 2
1.00
3.10
f1 (ppm)

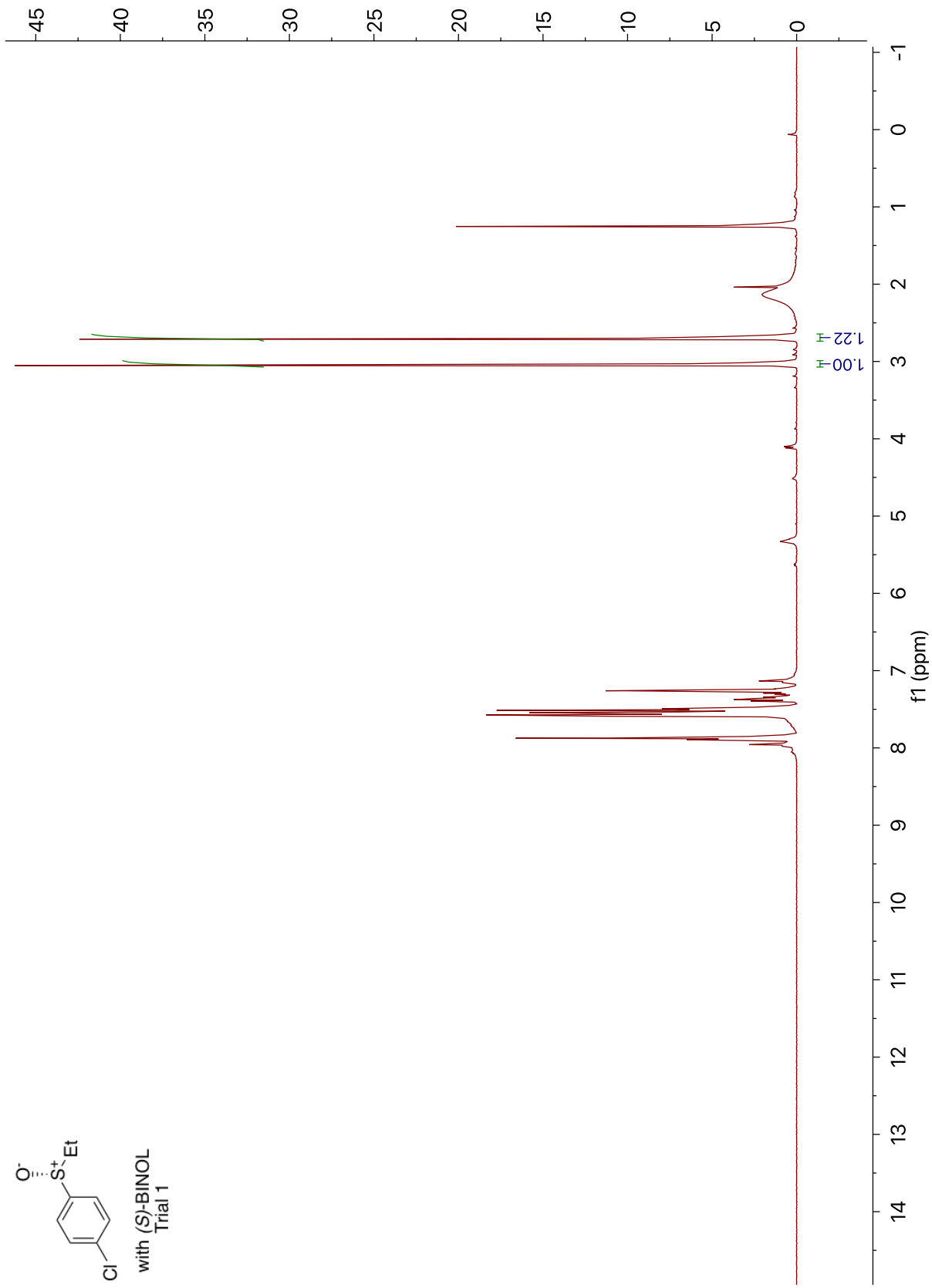

O
S+
iPr
Me
with (R)-BINOL
Trial 2
85.06
1.00
f1 (ppm)

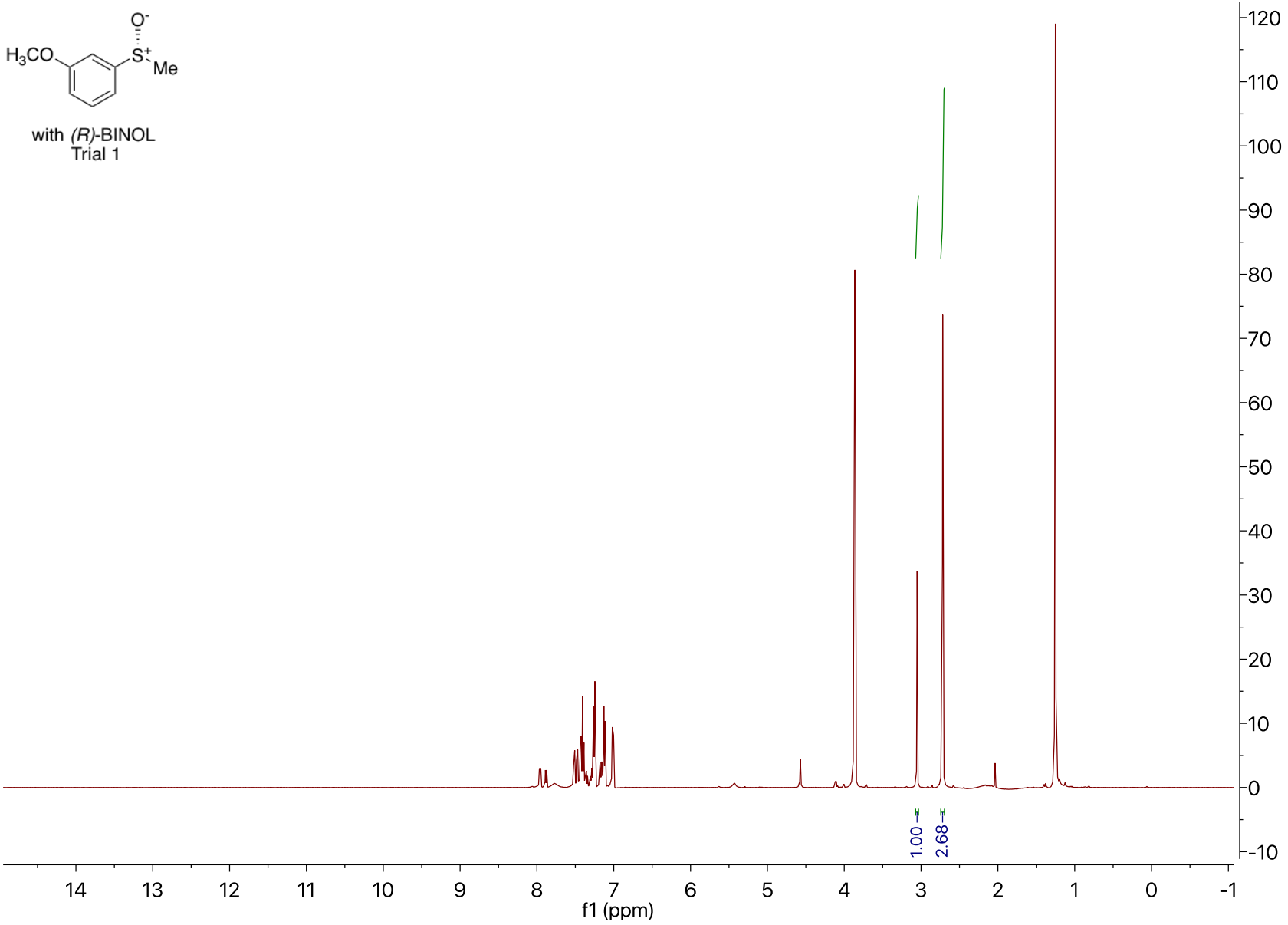

O⁻
S⁺
iPr
Me
with (S)-BINOL
Trial 2
1.00
176.42
f1 (ppm)


Br
O
S+
Me
with (R)-BINOL
Trial 1
1.00
3.35
f1 (ppm)

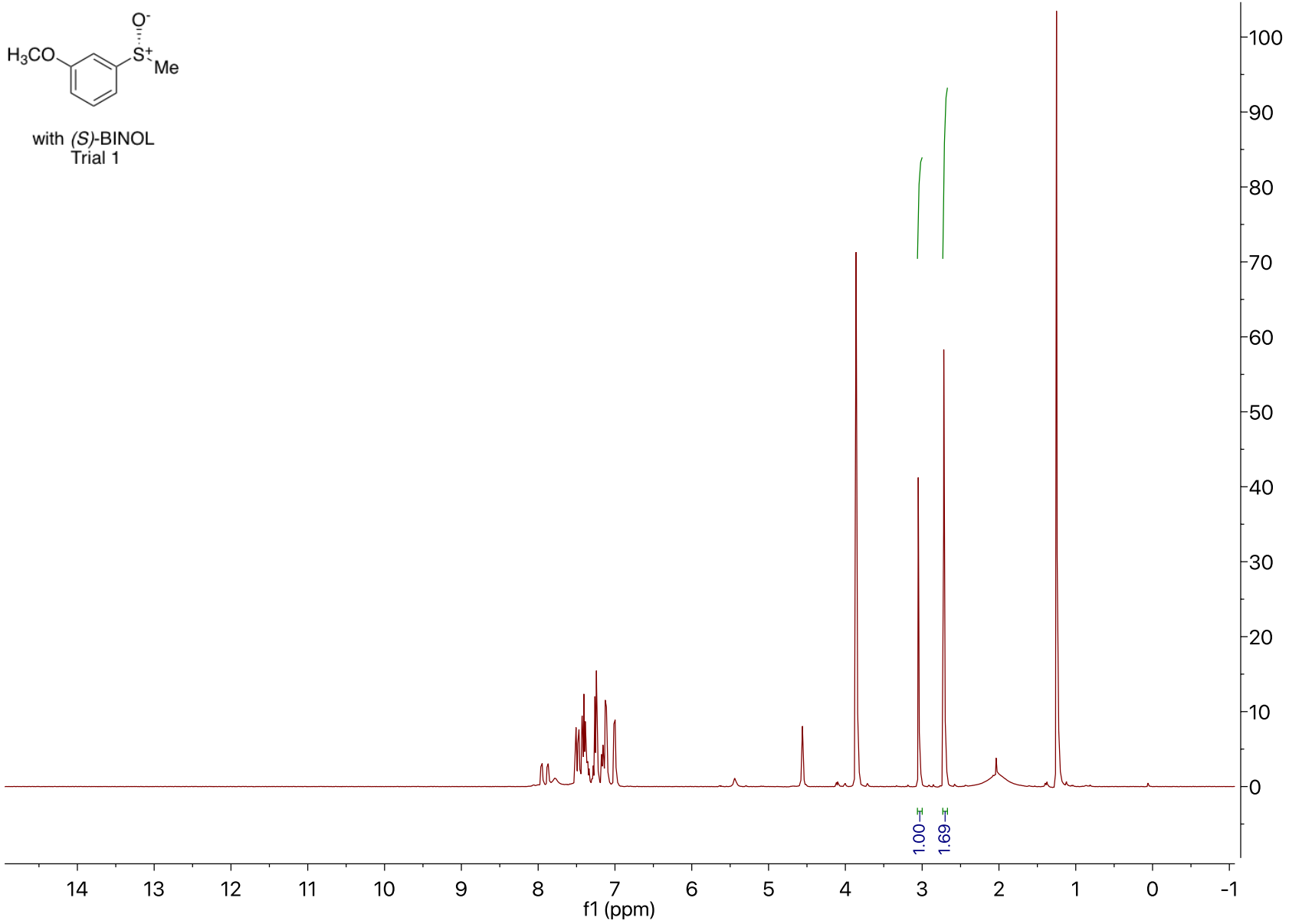

Br
O
S+
Me
with (S)-BINOL
Trial 1
1.00
1.01
f1 (ppm)

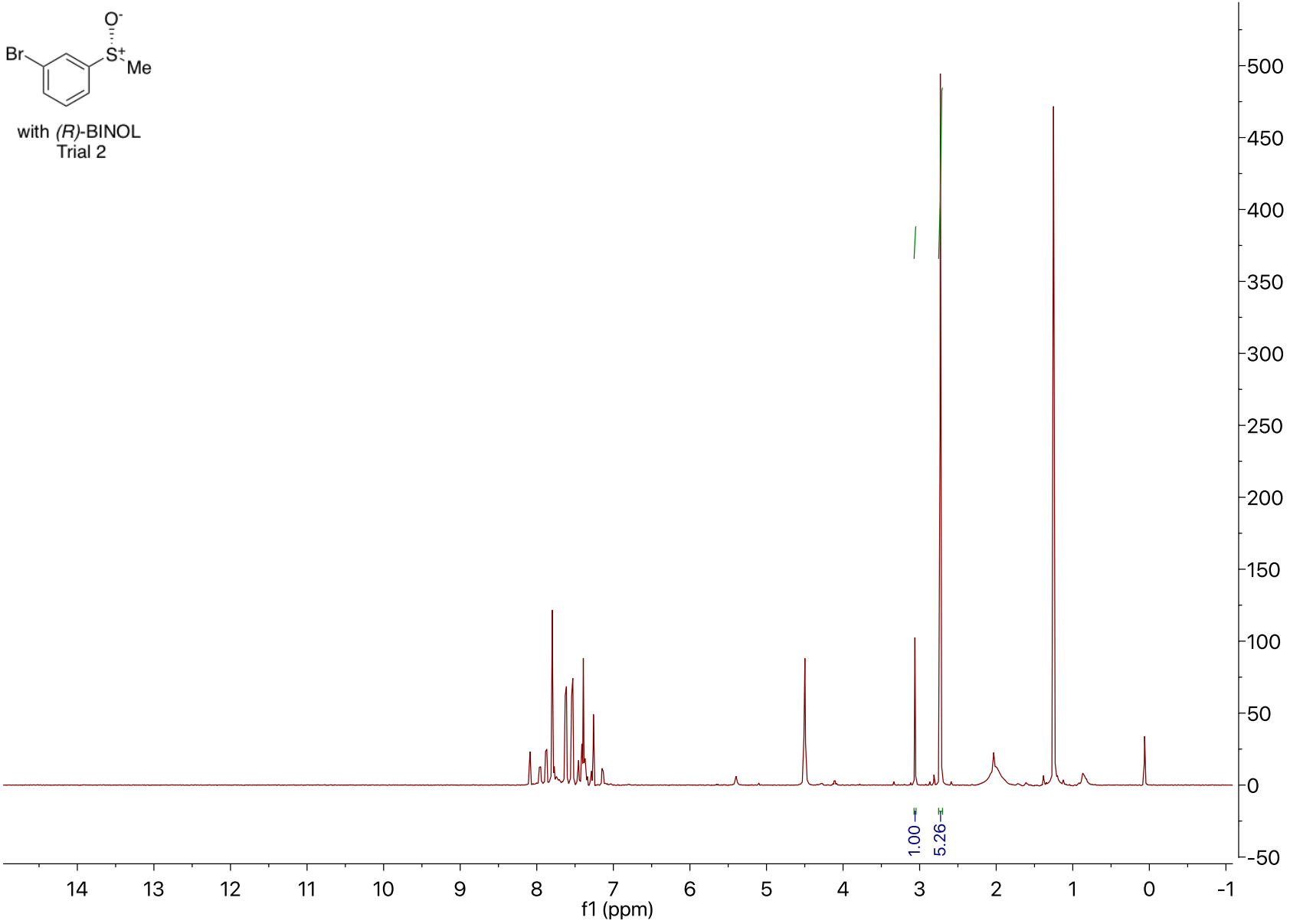

O-
S+
Me
Cl
with (R)-BINOL
Trial 1
88
1.00
2.07
f1 (ppm)

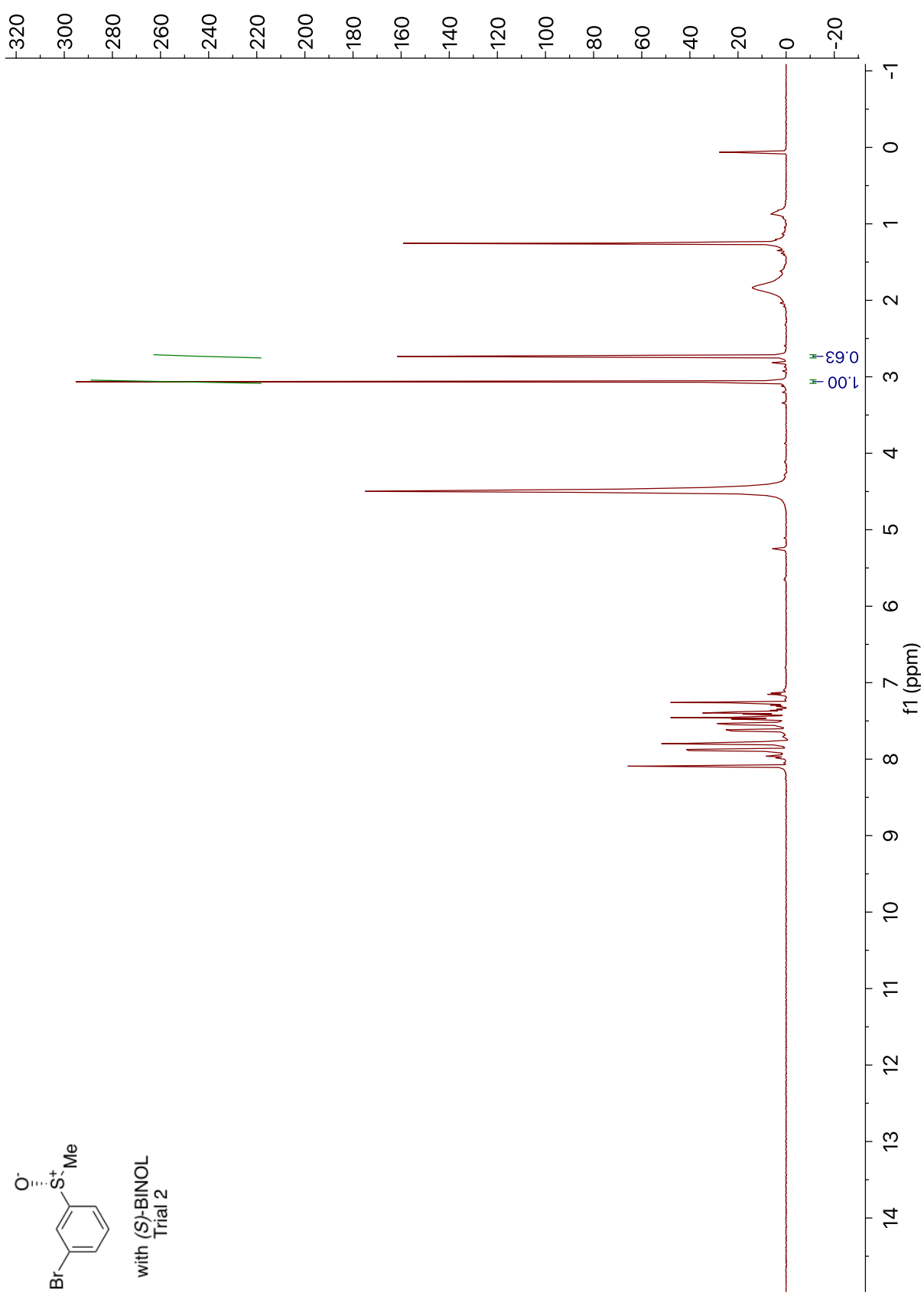

O
S
Et
Cl
with (S)-BINOL
Trial 1
1.22
1.00
f1 (ppm)

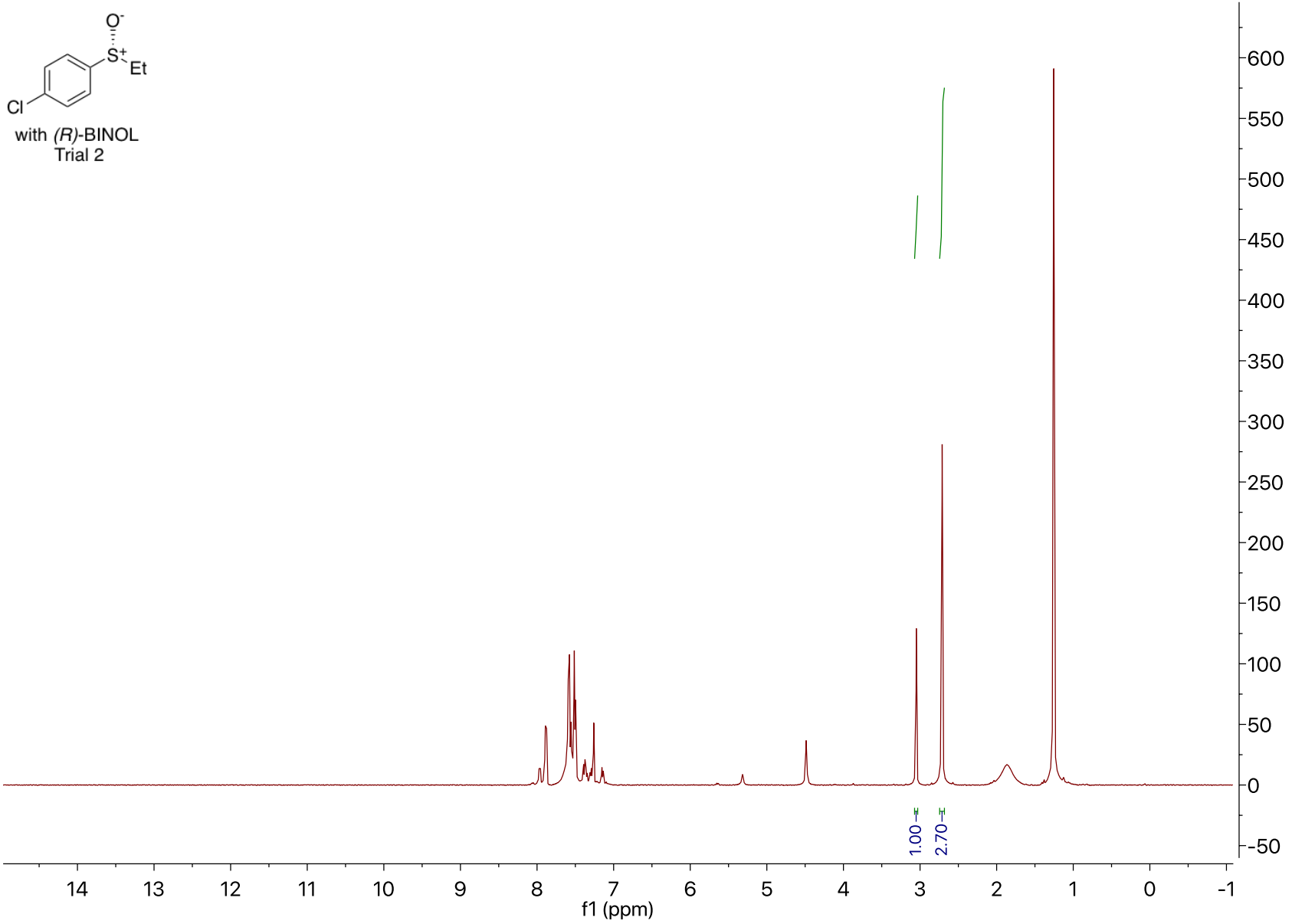


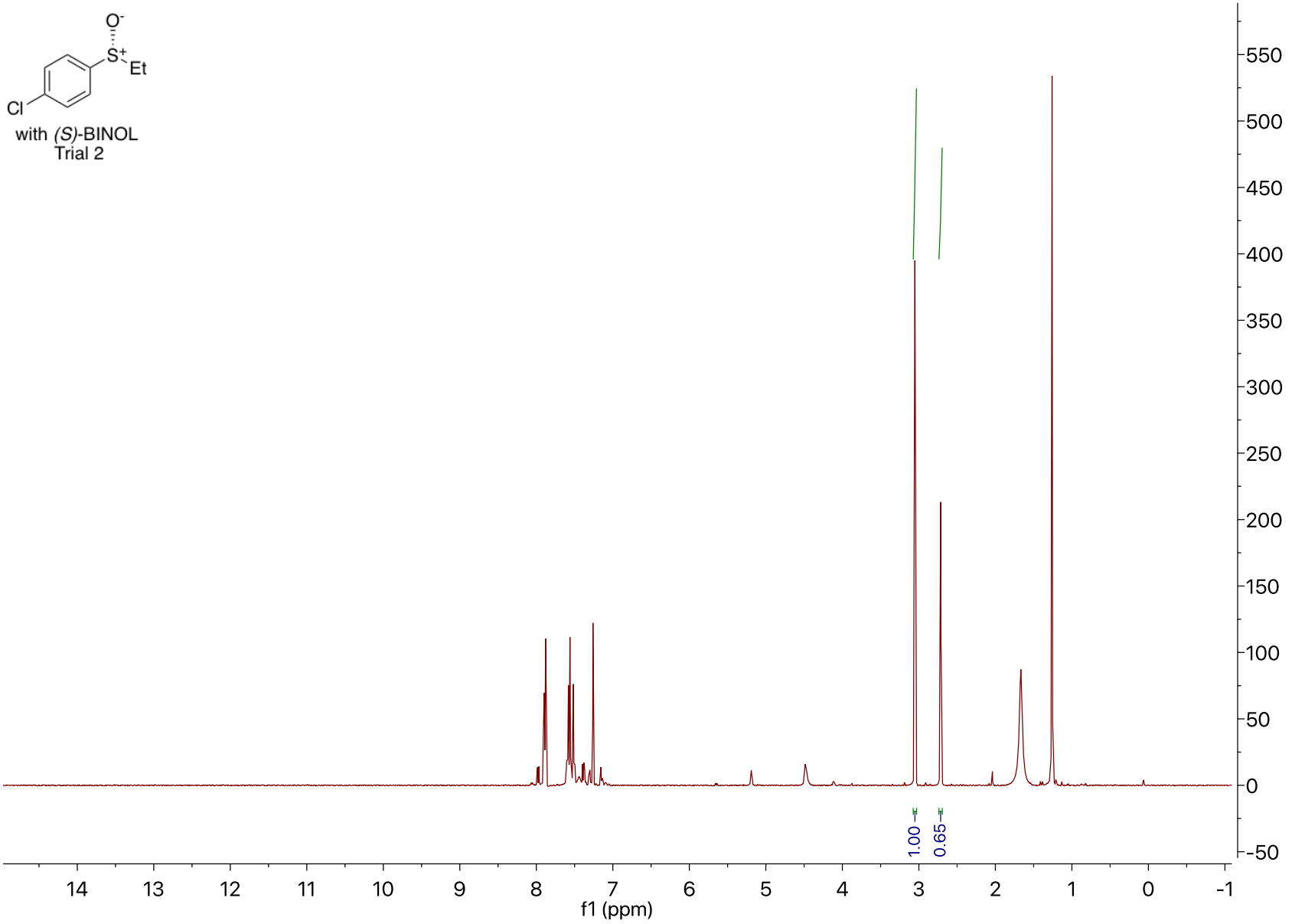
90

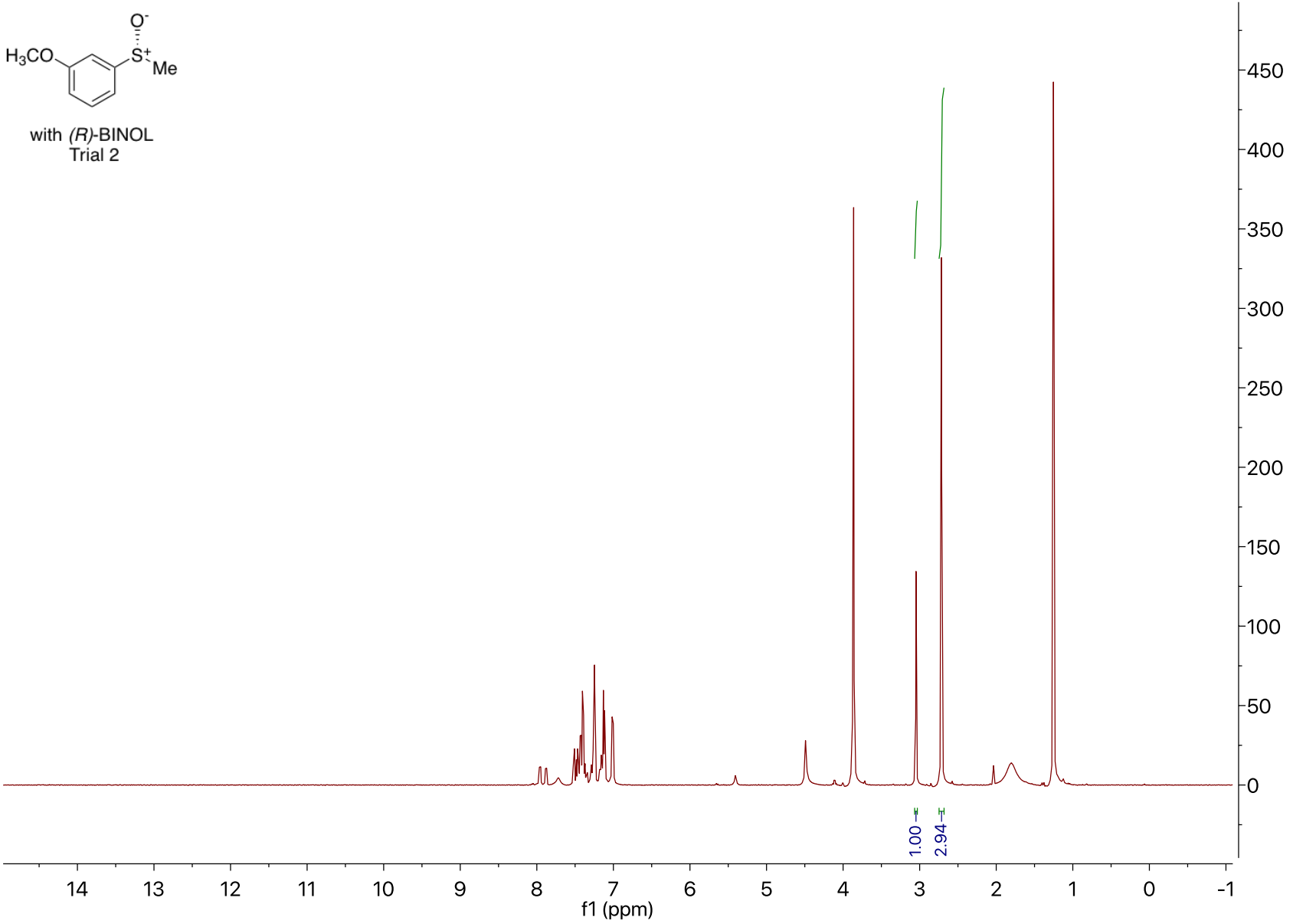

H3CO
O-
S+
Me
with (S)-BINOL
Trial 1
1.00
1.69
f1 (ppm)

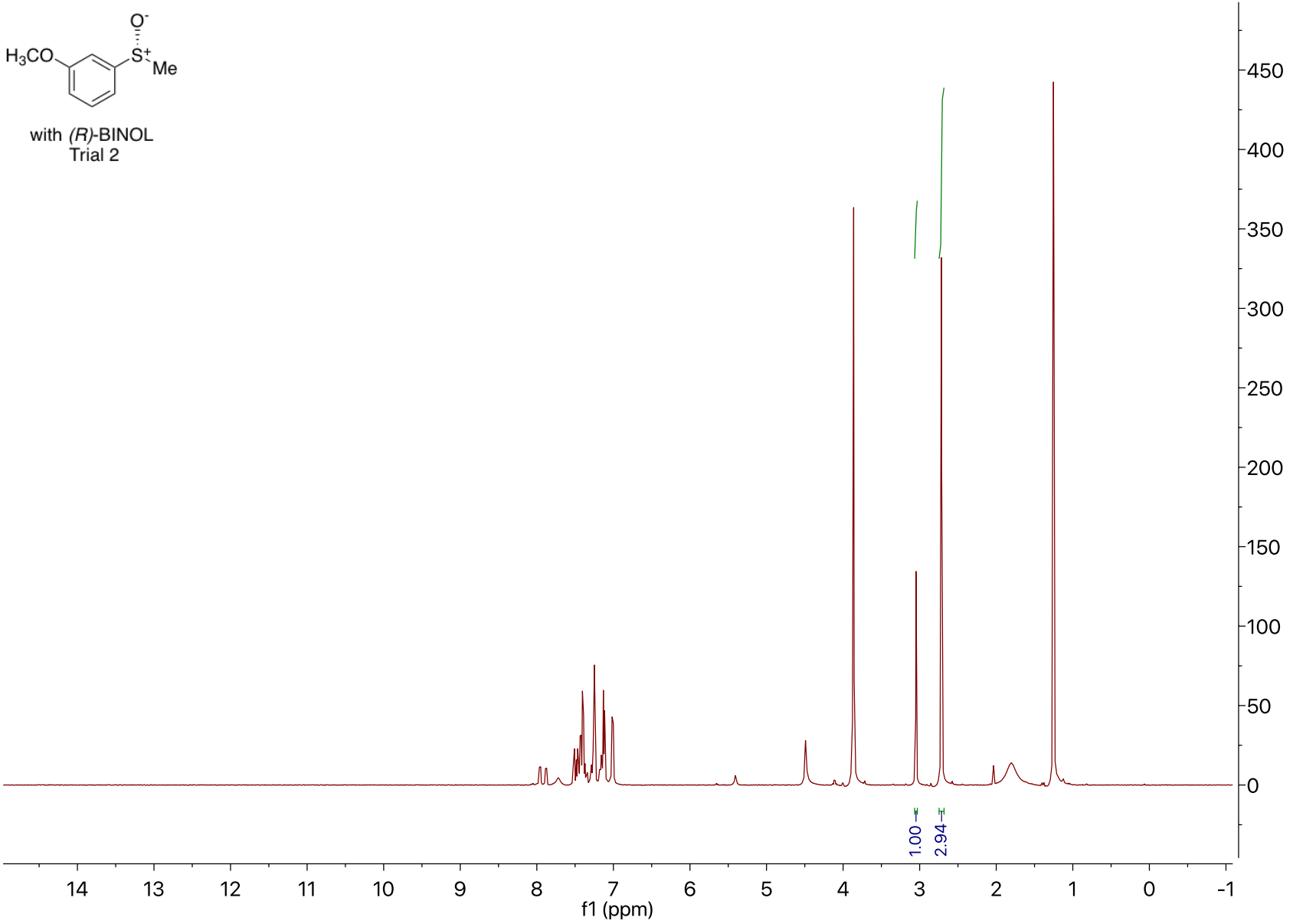

Br
O
S+
Me
with (R)-BINOL
Trial 2
1.00
5.26
f1 (ppm)


with (S)-BINOL
Trial 2
Br
O
S
Me
f1 (ppm)
1.00
0.63


O-
S+
Et
Cl
with (R)-BINOL
Trial 2
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
1.00
2.70
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

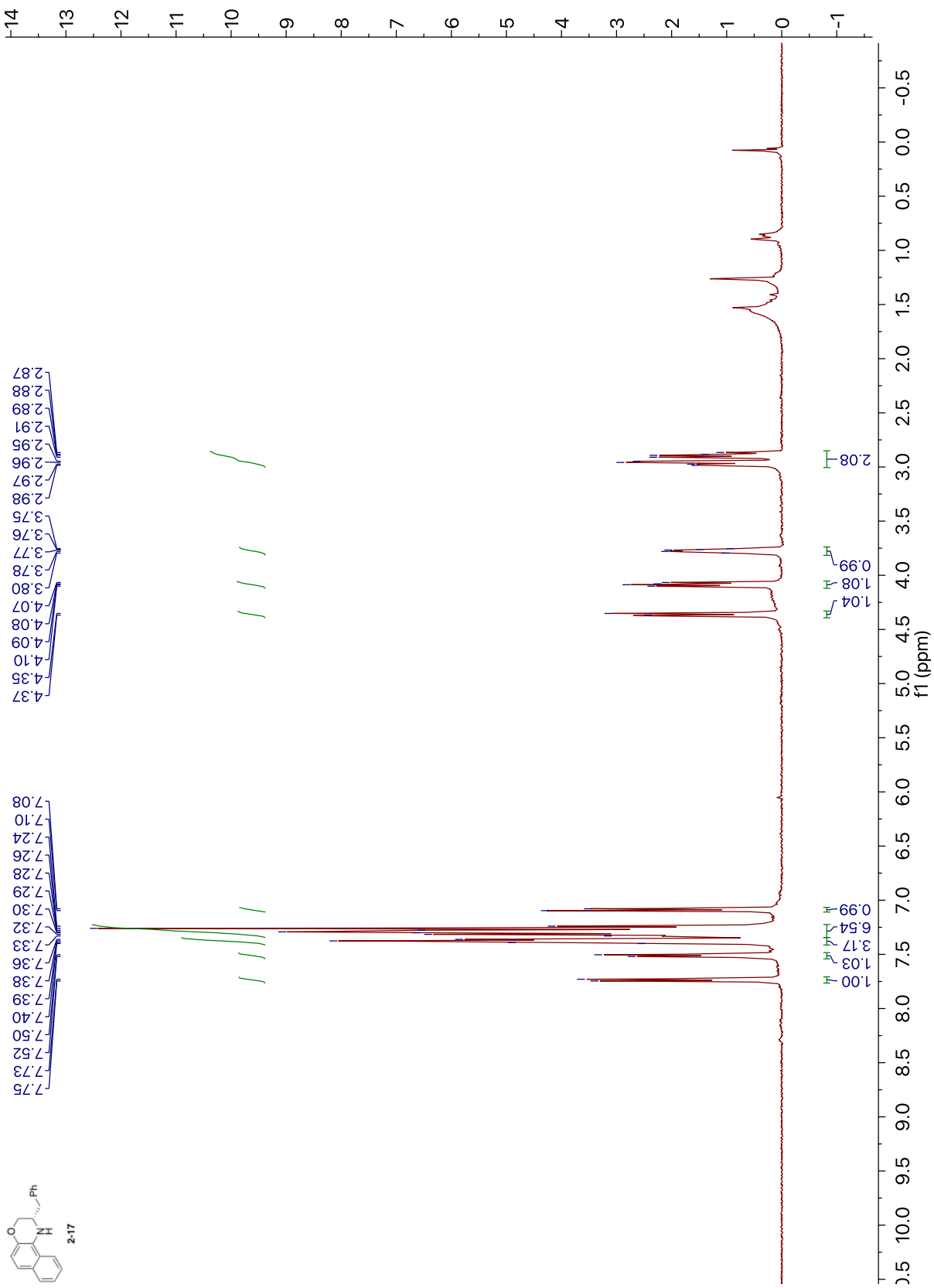

O-
S+
Et
Cl
with (S)-BINOL
Trial 2
1.00
0.65
f1 (ppm)

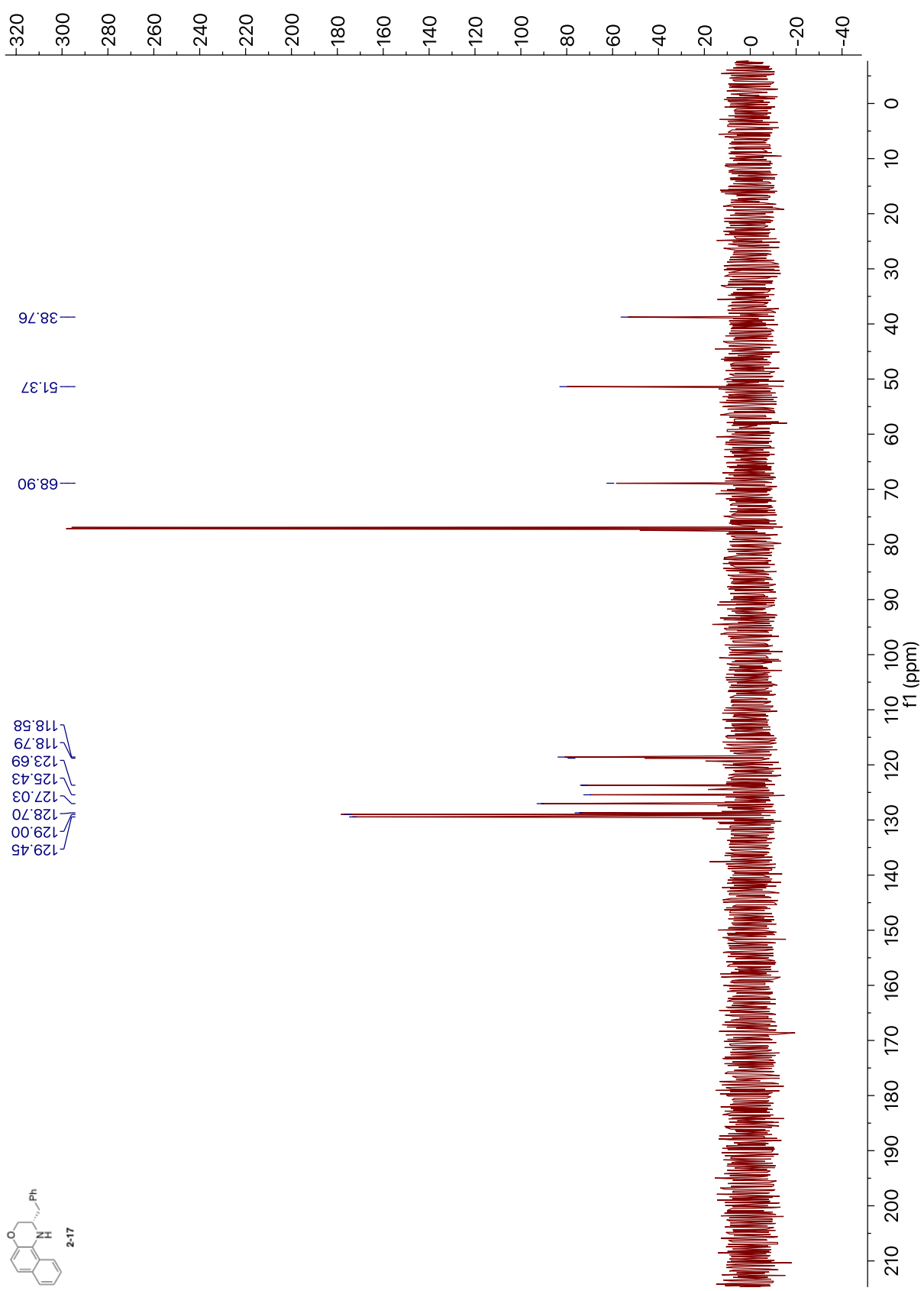

H3CO
O-
S+
Me
with (R)-BINOL
Trial 2
96
1.00
2.94
f1 (ppm)

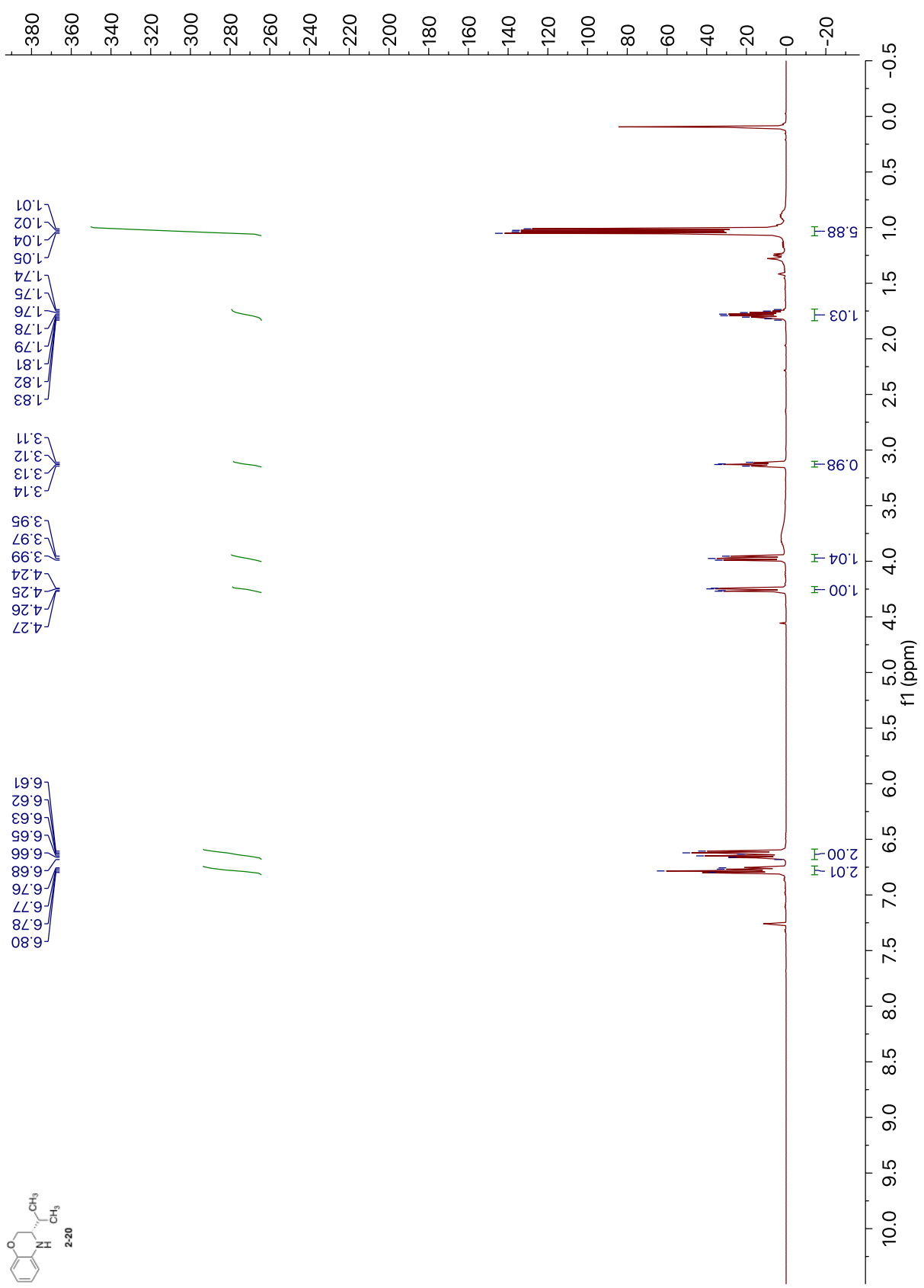

O⁻
H3CO
S+
Me
with (R)-BINOL
Trial 2
450
400
350
300
250
200
150
100
50
0
1.00
2.94
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

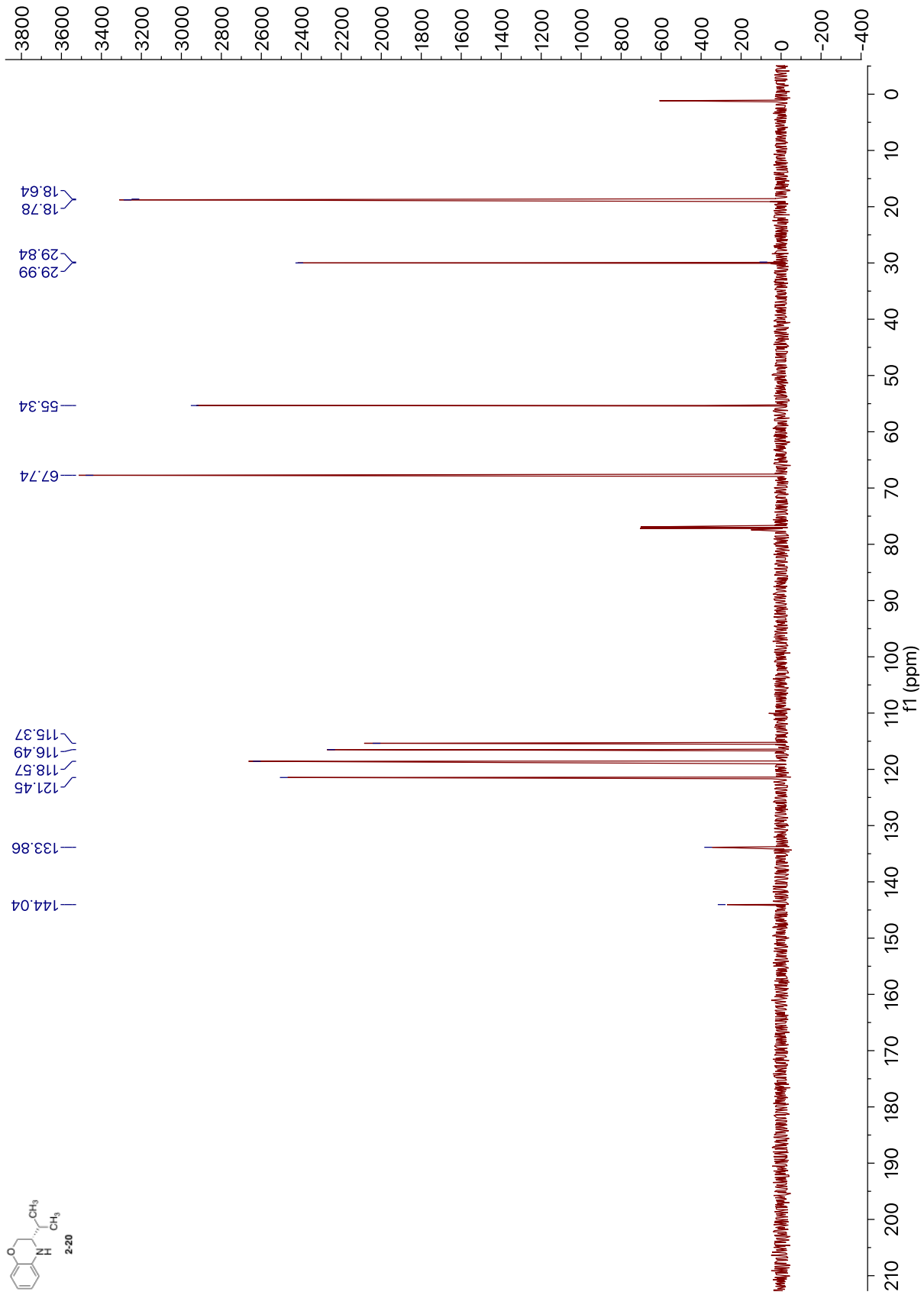
Appendix B:

NMR Spectra of Novel Compounds for Chapter 2


2-17
Ph
O
N
H
7.75
7.73
7.52
7.50
7.40
7.39
7.38
7.36
7.33
7.32
7.30
7.29
7.28
7.26
7.24
7.10
7.08
4.37
4.35
4.10
4.09
4.08
4.07
3.80
3.78
3.77
3.76
3.75
2.98
2.97
2.96
2.95
2.91
2.89
2.88
2.87
1.00
1.03
3.17
6.54
0.99
2.08
0.99
1.08
1.04
f1 (ppm)

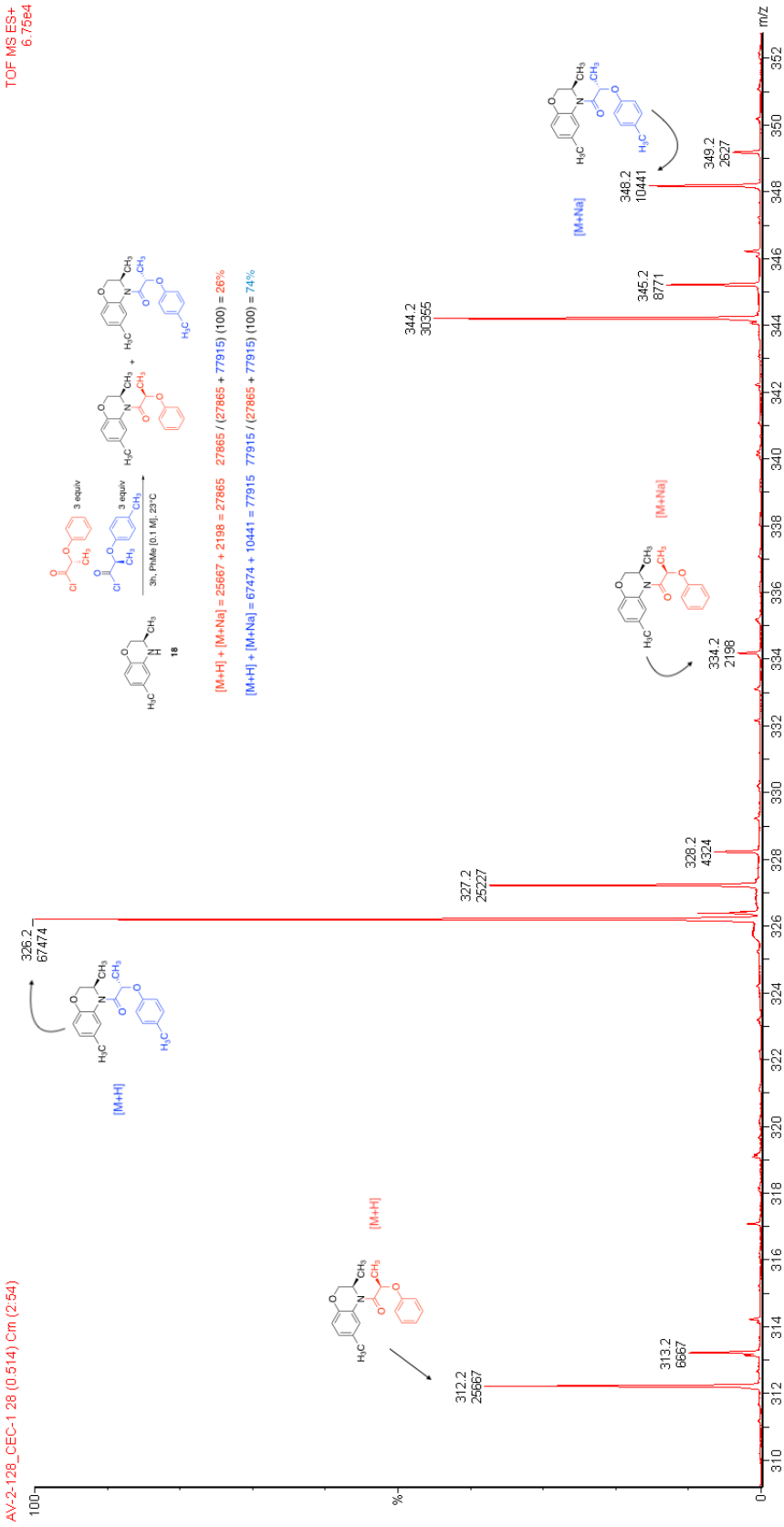

38.76
51.37
68.90
118.58
118.79
123.69
125.43
127.03
128.70
129.00
129.45
f1 (ppm)
2-17

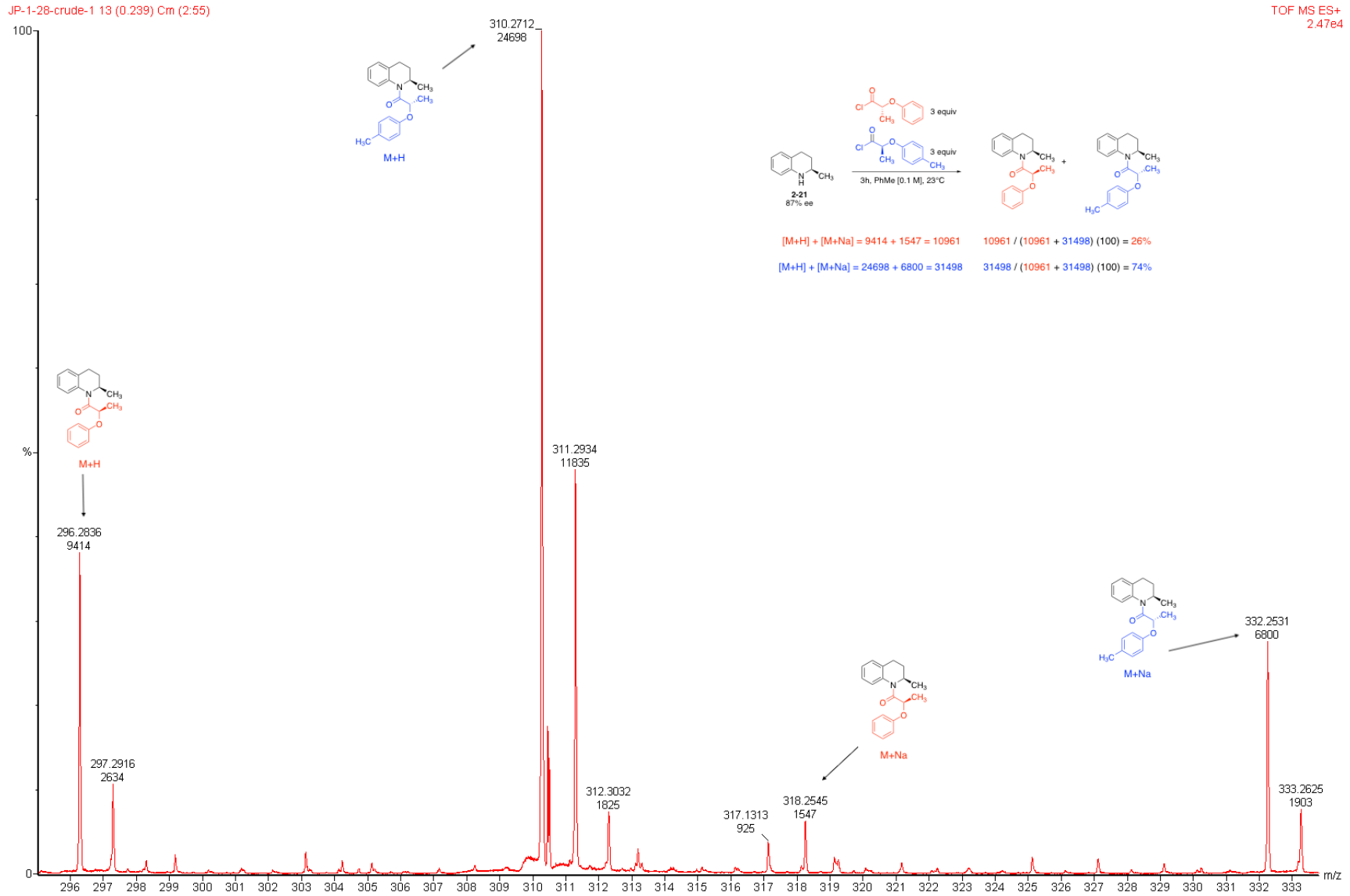

1.01
1.02
1.04
1.05
1.74
1.75
1.76
1.78
1.79
1.81
1.82
1.83
3.11
3.12
3.13
3.14
3.95
3.97
3.99
4.24
4.25
4.26
4.27
6.61
6.62
6.63
6.65
6.66
6.68
6.76
6.77
6.78
6.80
5.88
1.03
0.98
1.04
1.00
2.00
2.01
f1 (ppm)
2-20

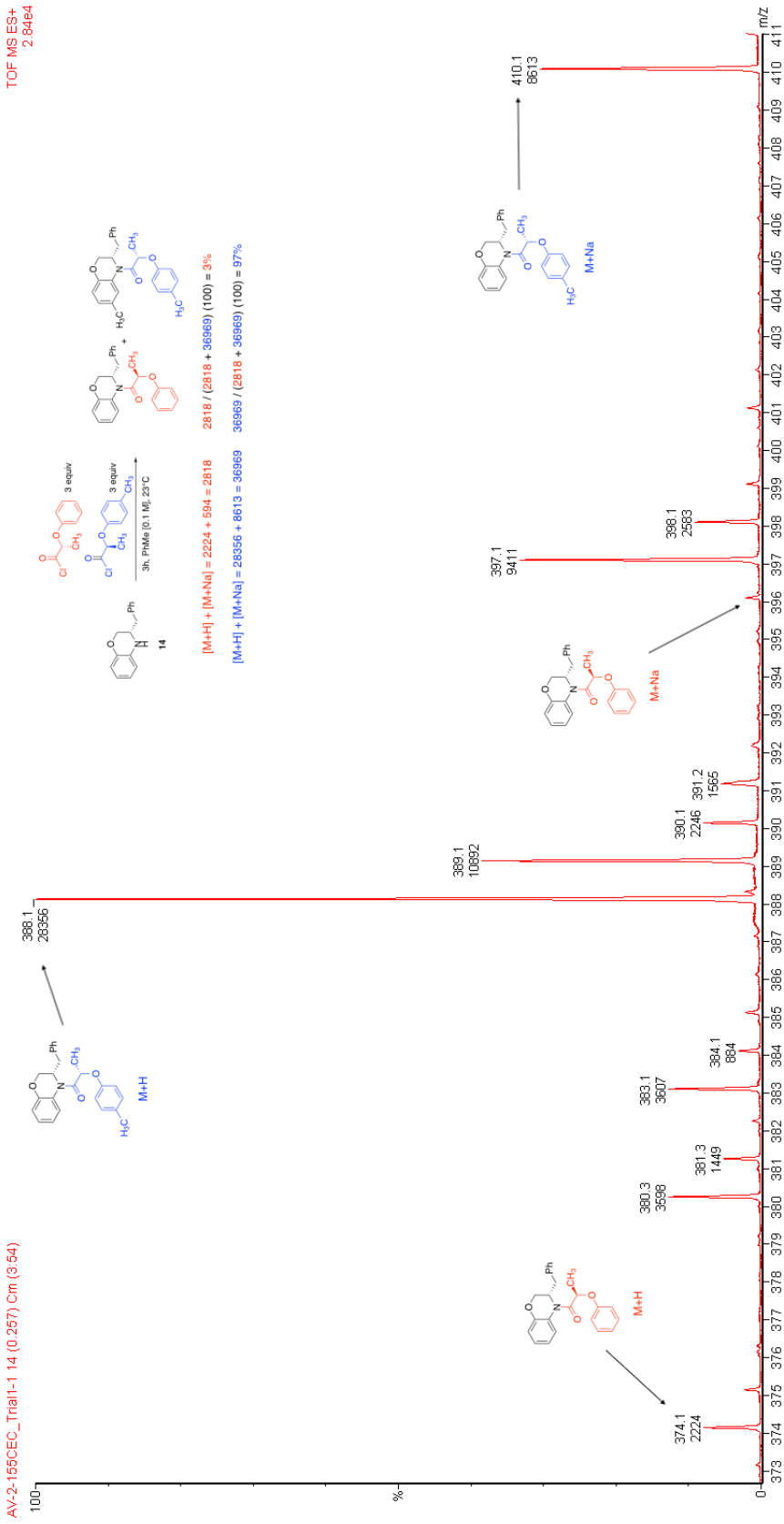

18.64
18.78
29.84
29.99
55.34
67.74
115.37
116.49
118.57
121.45
133.86
144.04
f1 (ppm)

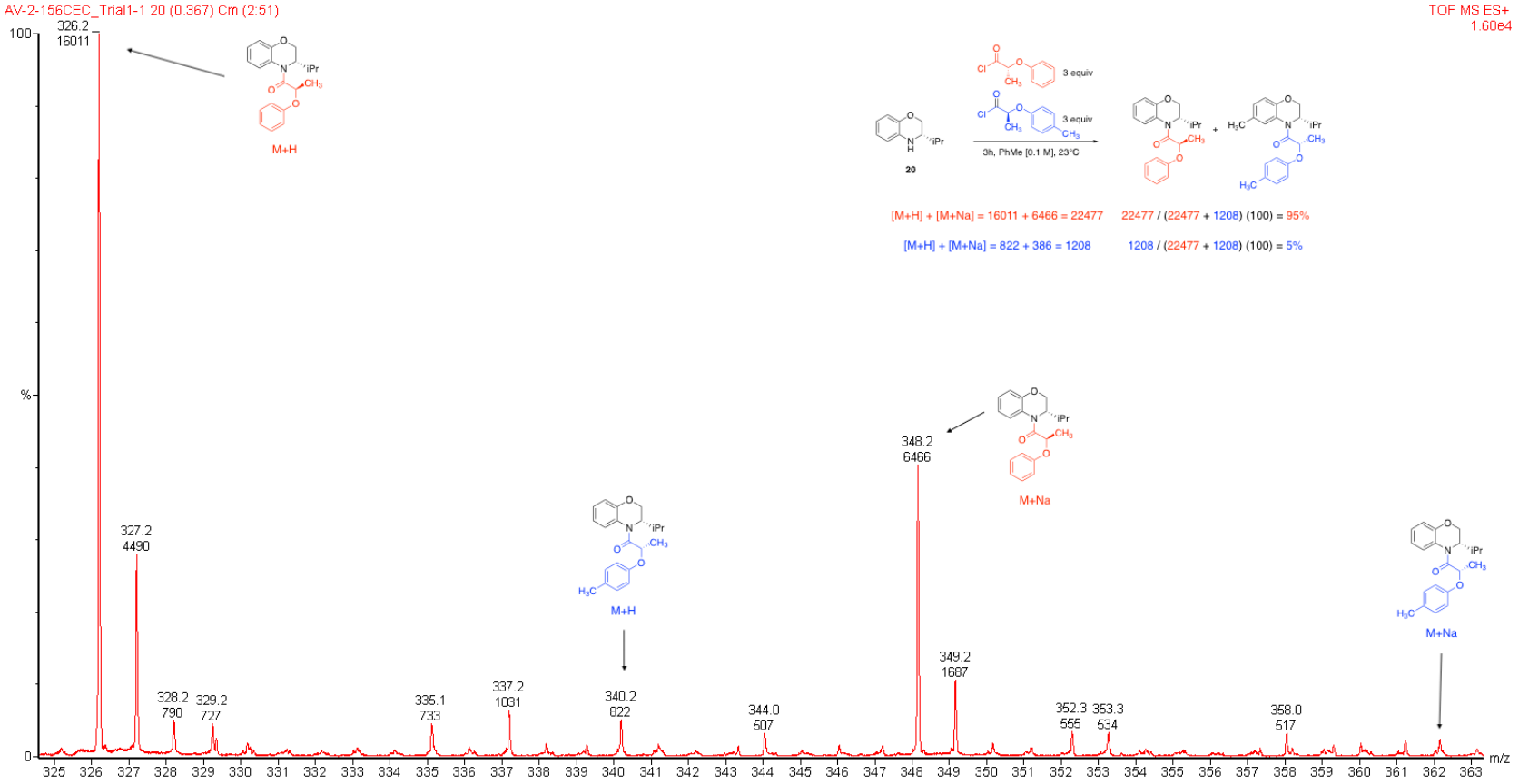
Appendix B:

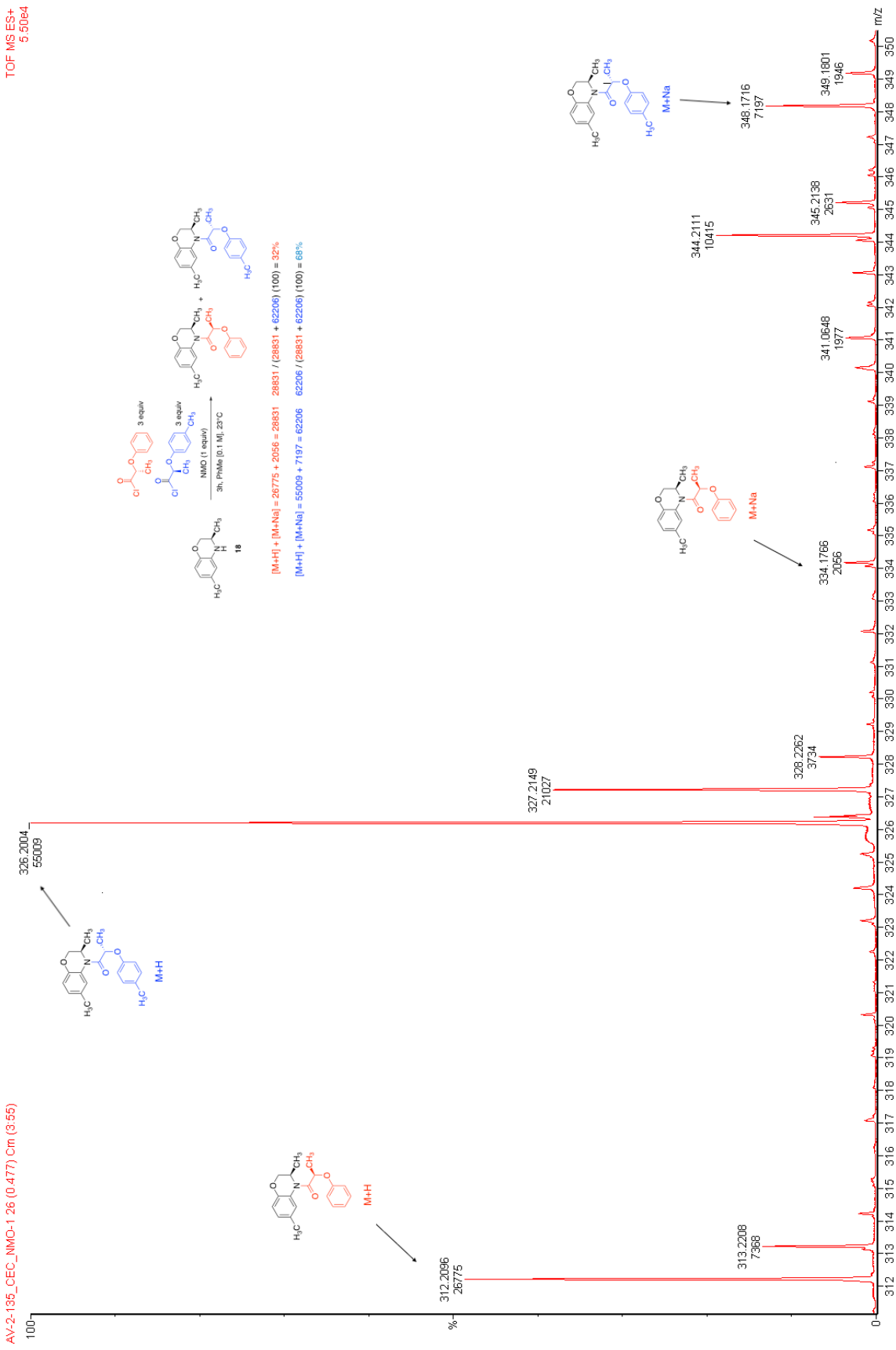
MS Spectra of CEC Experiments for Chapter 2

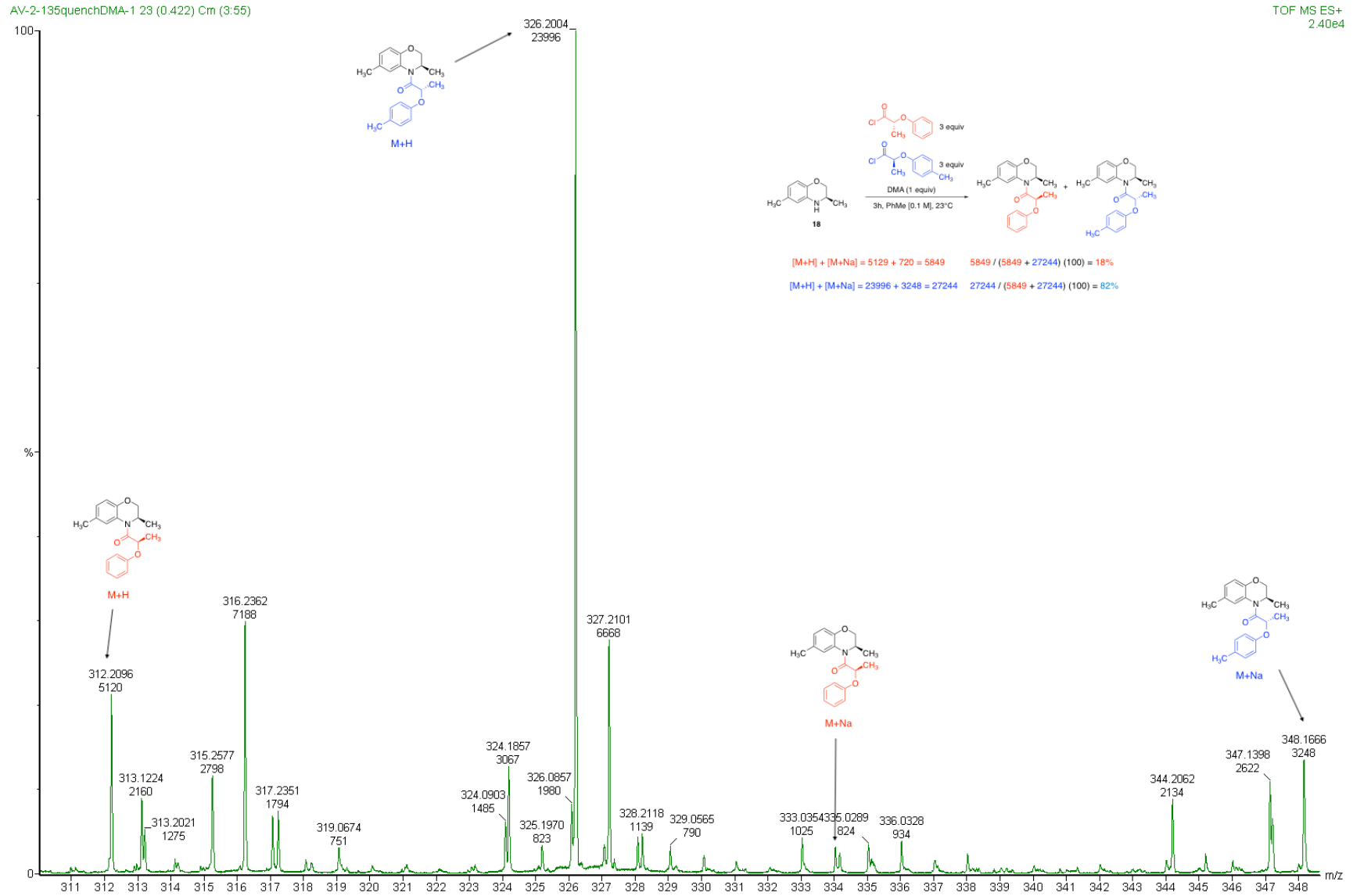

TOF MS ES+
6.75e4
AV-2-128_CEC-1 28 (0.514) Cm (2:54)
100
%
0
m/z
310
312
314
316
318
320
322
324
326
328
330
332
334
336
338
340
342
344
346
348
350
352
312.2
25667
313.2
6667
326.2
67474
327.2
25227
328.2
4324
334.2
2198
344.2
30355
345.2
8771
348.2
10441
349.2
2627
[M+H]
[M+Na]
3 equiv
3 equiv
3h, PhMe (0.1 M), 23°C
18
[M+H] + [M+Na] = 25667 + 2198 = 27865 27865 / (27865 + 77915) (100) = 26%
[M+H] + [M+Na] = 67474 + 10441 = 77915 77915 / (27865 + 77915) (100) = 74%

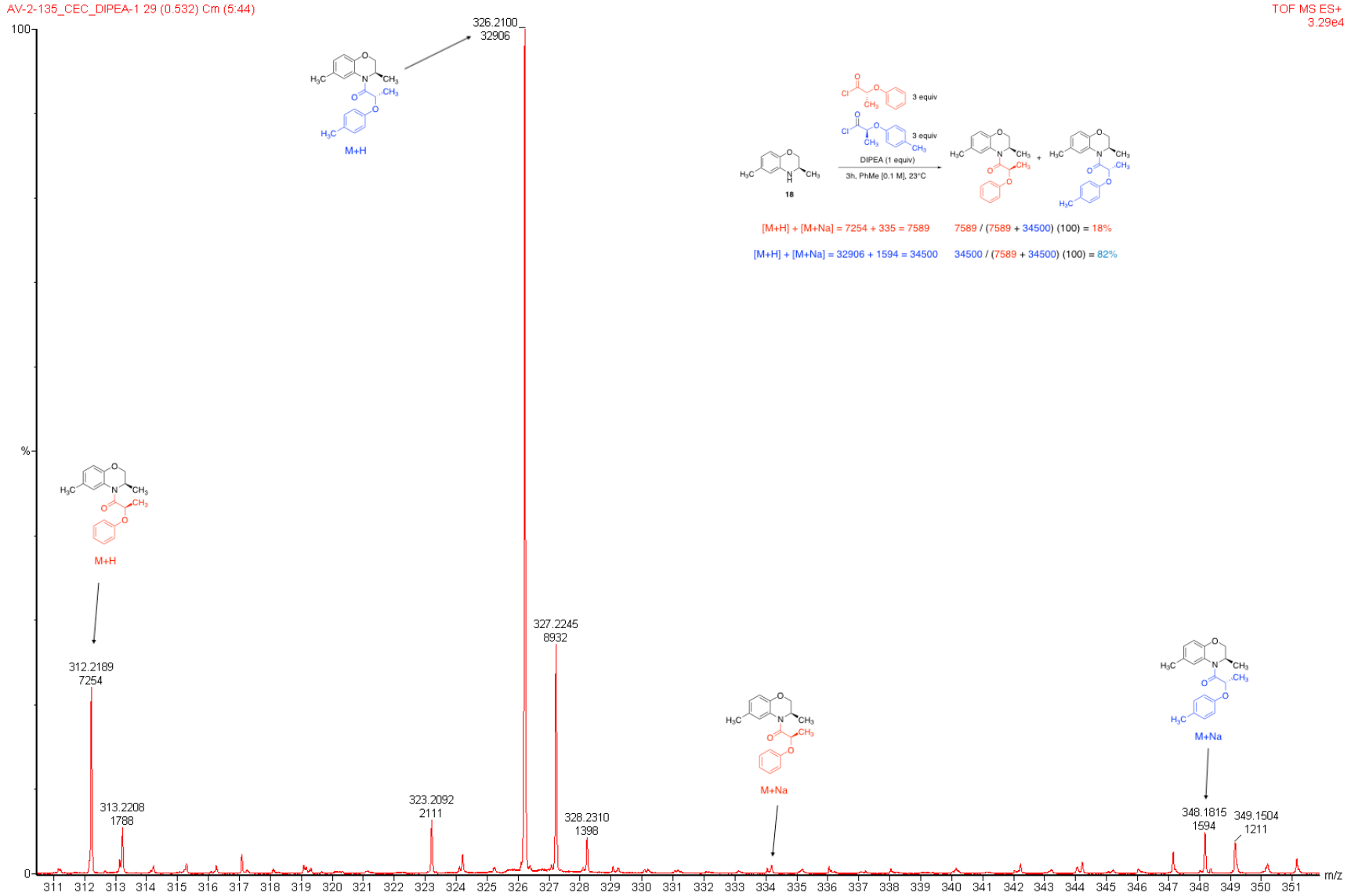

JP-1-28-crude-1 13 (0.239) Cm (2:55)
TOF MS ES+
2.47e4
100
%
0
310.2712
24698
M+H
311.2934
11835
296.2836
9414
M+H
297.2916
2634
312.3032
1825
317.1313
925
318.2545
1547
M+Na
332.2531
6800
M+Na
333.2625
1903
m/z
296 297 298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333
2-21
87% ee
3 equiv
3 equiv
3h, PhMe [0.1 M], 23°C
[M+H] + [M+Na] = 9414 + 1547 = 10961
10961 / (10961 + 31498) (100) = 26%
[M+H] + [M+Na] = 24698 + 6800 = 31498
31498 / (10961 + 31498) (100) = 74%

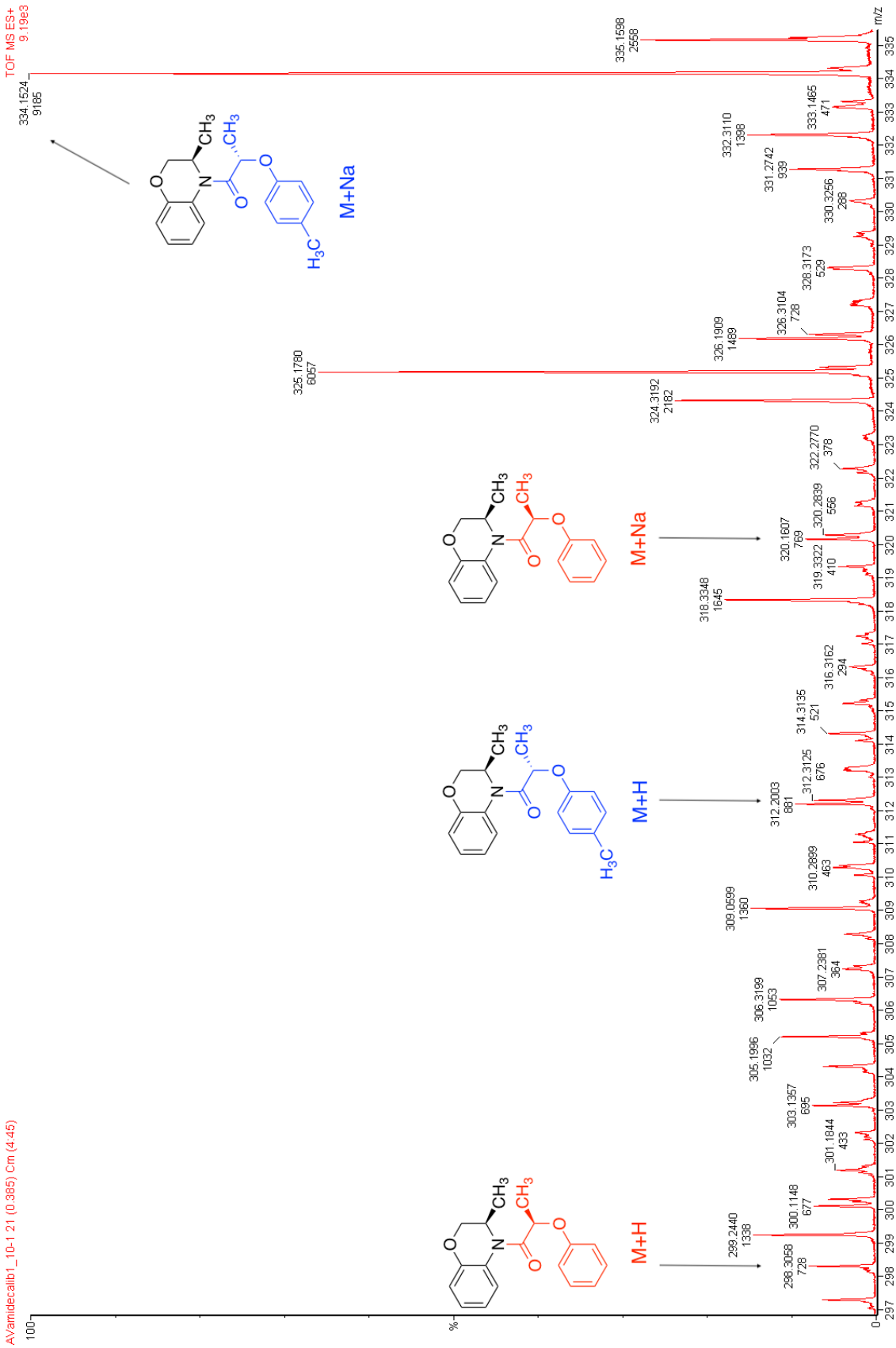

TOF MS ES+
2.84e4
AV-2-155CEC_Trial1-1 14 (0.257) Cm (3:54)
100
%
0
m/z
373 374 375 376 377 378 379 380 381 382 383 384 385 386 387 388 389 390 391 392 393 394 395 396 397 398 399 400 401 402 403 404 405 406 407 408 409 410 411
374.1
2224
380.3
3698
381.3
1449
383.1
3607
384.1
884
388.1
28356
389.1
10692
390.1
2246
391.2
1565
397.1
9411
398.1
2583
410.1
8613
M+H
M+H
M+Na
M+Na
3 equiv
3 equiv
3h, PhMe (0.1 M), 23°C
14
[M+H] + [M+Na] = 2224 + 594 = 2818
2818 / (2818 + 36969) (100) = 3%
[M+H] + [M+Na] = 28356 + 8613 = 36969
36969 / (2818 + 36969) (100) = 97%

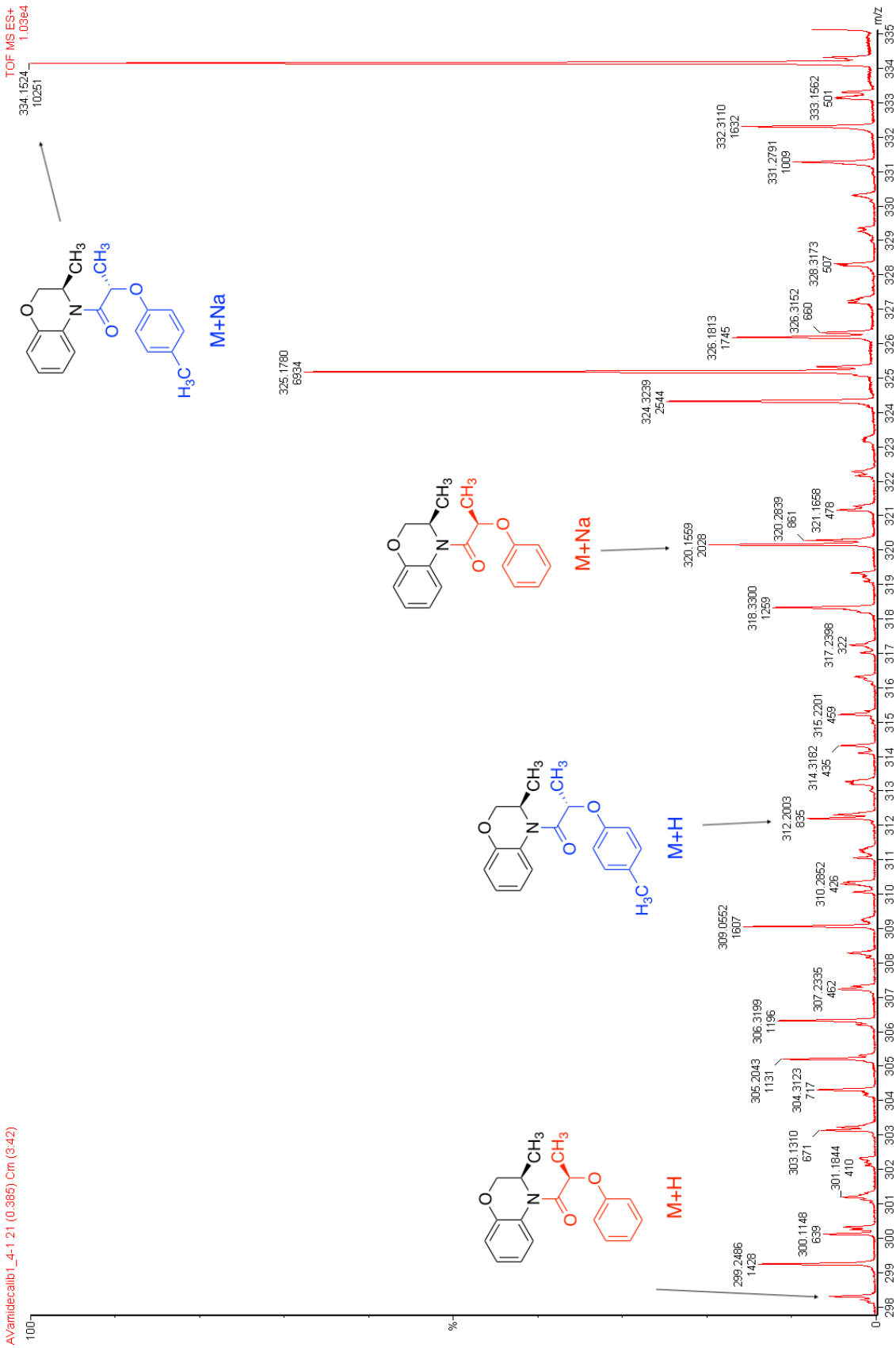

AV-2-156CEC_Trial1-1 20 (0.367) Cm (2:51)
TOF MS ES+
1.60e4
100
%
0
326.2
16011
M+H
327.2
4490
328.2
790
329.2
727
335.1
733
337.2
1031
340.2
822
M+H
344.0
507
348.2
6466
M+Na
349.2
1687
352.3
555
353.3
534
358.0
517
M+Na
m/z
325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351 352 353 354 355 356 357 358 359 360 361 362 363
20
3 equiv
3 equiv
3h, PhMe [0.1 M], 23°C
[M+H] + [M+Na] = 16011 + 6466 = 22477
22477 / (22477 + 1208) (100) = 95%
[M+H] + [M+Na] = 822 + 386 = 1208
1208 / (22477 + 1208) (100) = 5%

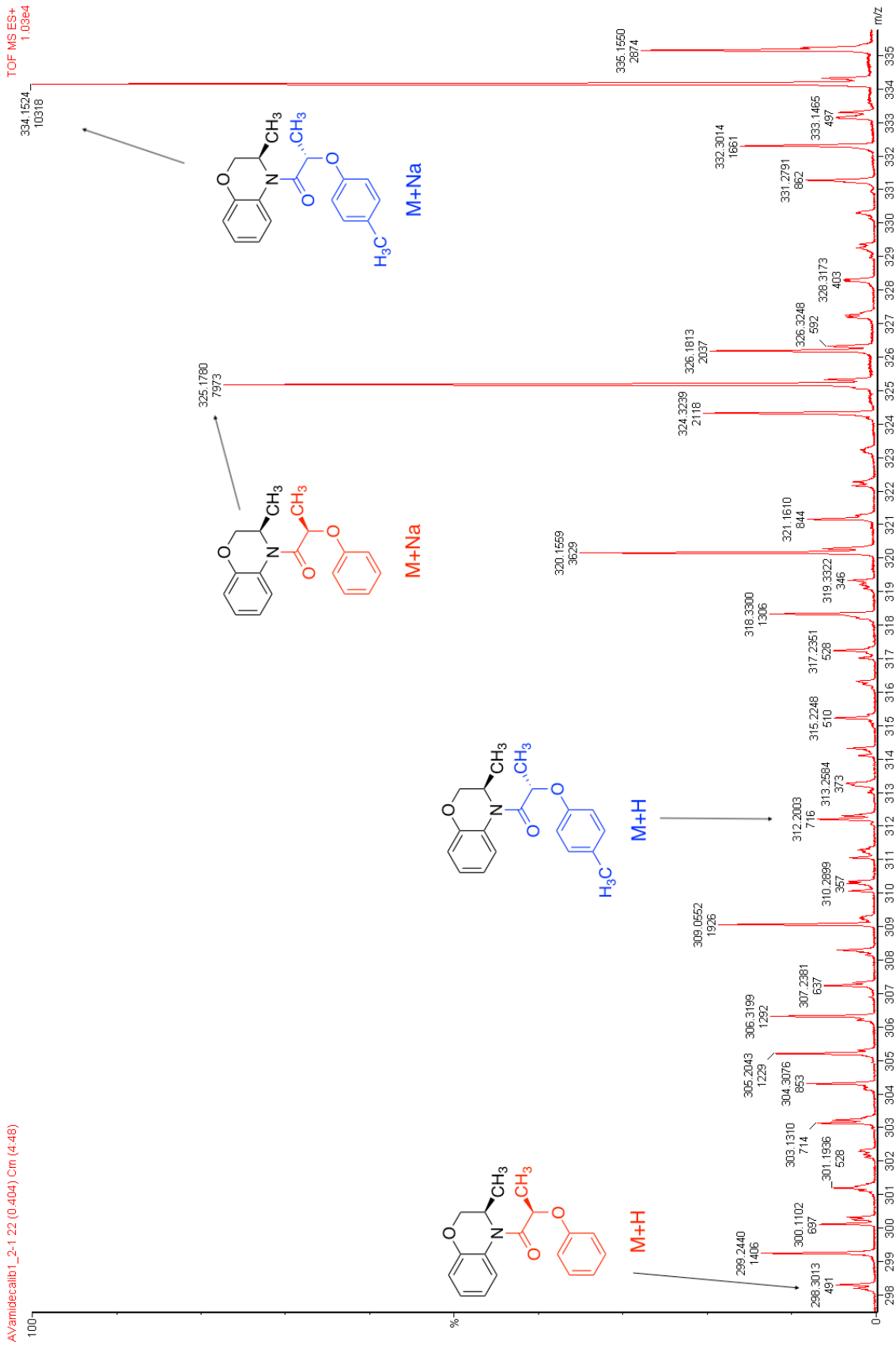

TOF MS ES+
5.50e4
AV-2-135_CEC_NMO-1 26 (0.477) Cm (3:55)
100
%
0
m/z
312.2096
26775
313.2208
7368
326.2004
55009
327.2149
21027
328.2262
3734
334.1766
2056
341.0648
1977
344.2111
10415
345.2138
2631
348.1716
7197
349.1801
1946
M+H
M+Na
3 equiv
3 equiv
NMO (1 equiv)
3h, PhMe (0.1 M), 23°C
18
[M+H] + [M+Na] = 26775 + 2056 = 28831 28831 / (28831 + 62206) (100) = 32%
[M+H] + [M+Na] = 55009 + 7197 = 62206 62206 / (28831 + 62206) (100) = 68%

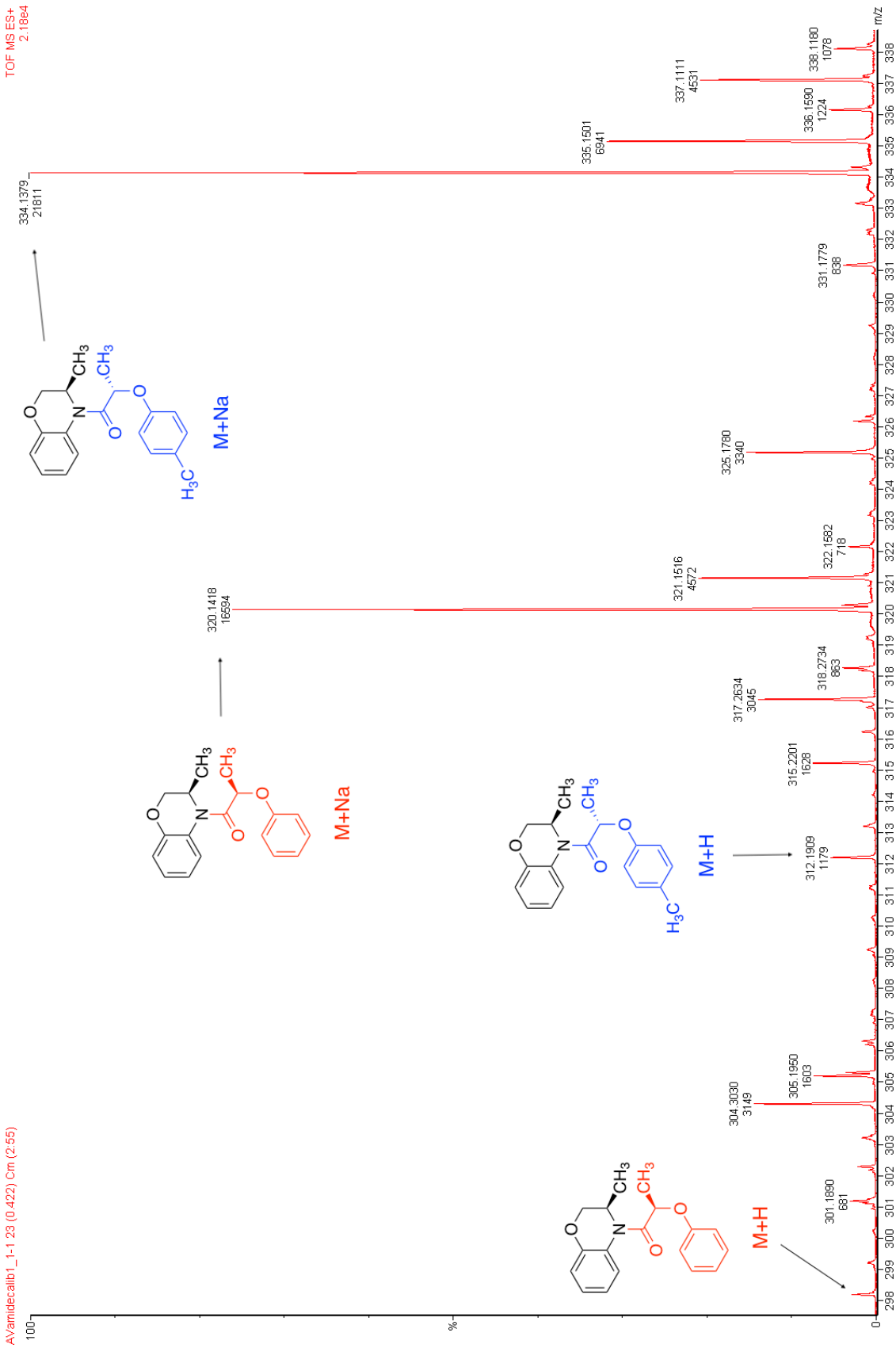

AV-2-135quenchDMA-1 23 (0.422) Cm (3:55)
TOF MS ES+
2.40e4
100
%
0
326.2004
23996
M+H
3 equiv
3 equiv
DMA (1 equiv)
3h, PhMe [0.1 M], 23°C
18
[M+H] + [M+Na] = 5129 + 720 = 5849
5849 / (5849 + 27244) (100) = 18%
[M+H] + [M+Na] = 23996 + 3248 = 27244
27244 / (5849 + 27244) (100) = 82%
M+H
312.2096
5120
313.1224
2160
313.2021
1275
315.2577
2798
316.2362
7188
317.2351
1794
319.0674
751
324.0903
1485
324.1857
3067
325.1970
823
326.0857
1980
327.2101
6668
328.2118
1139
329.0565
790
M+Na
333.0354
1025
335.0289
824
336.0328
934
M+Na
344.2062
2134
347.1398
2622
348.1666
3248
311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348
m/z

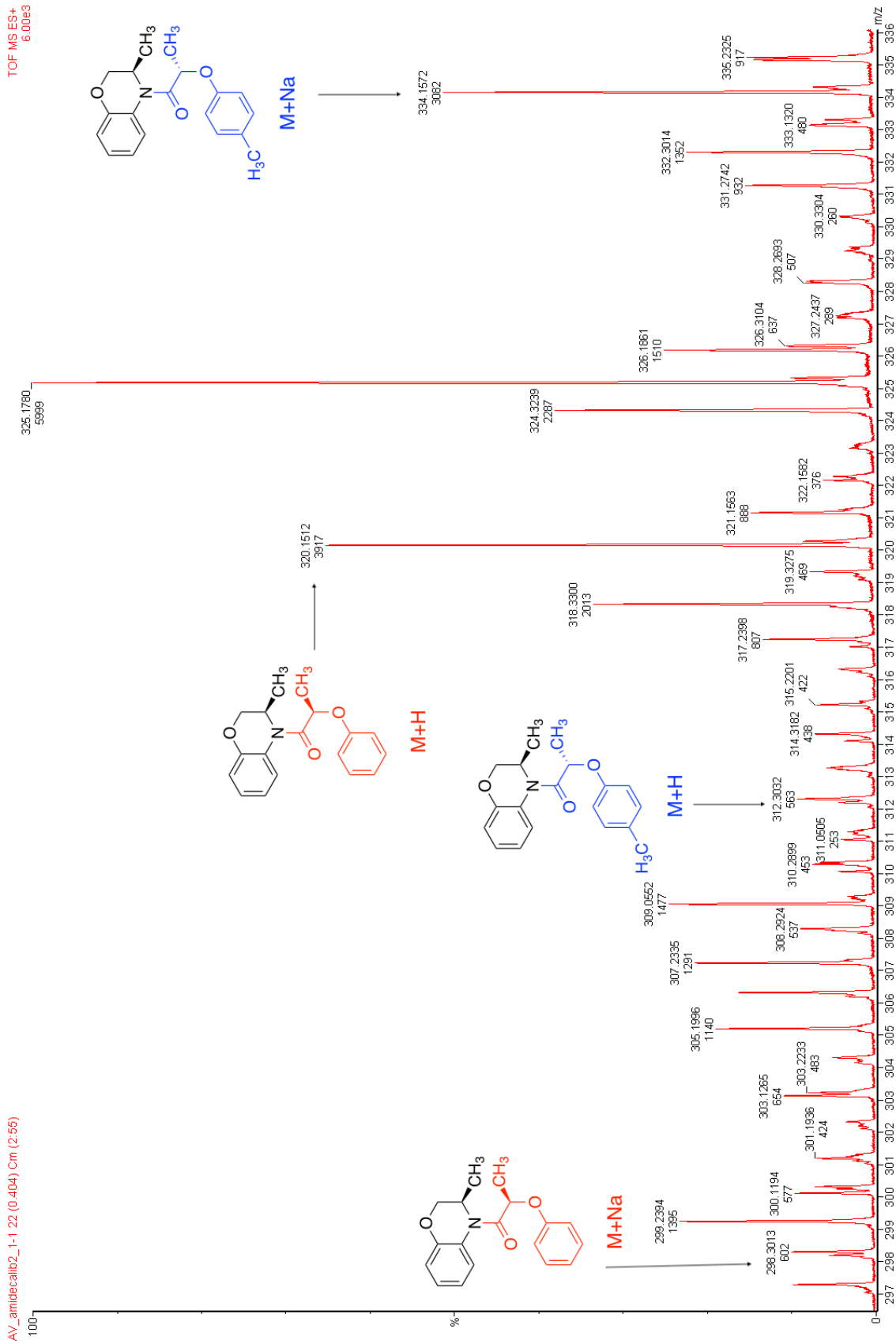

AV-2-135_CEC_DIPEA-1 29 (0.532) Cm (5:44)
TOF MS ES+
3.29e4
100
%
0
326.2100
32906
M+H
3 equiv
3 equiv
DIPEA (1 equiv)
3h, PhMe [0.1 M], 23°C
18
[M+H] + [M+Na] = 7254 + 335 = 7589
7589 / (7589 + 34500) (100) = 18%
[M+H] + [M+Na] = 32906 + 1594 = 34500
34500 / (7589 + 34500) (100) = 82%
M+H
312.2189
7254
313.2208
1788
323.2092
2111
327.2245
8932
328.2310
1398
M+Na
M+Na
348.1815
1594
349.1504
1211
311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338 339 340 341 342 343 344 345 346 347 348 349 350 351
m/z

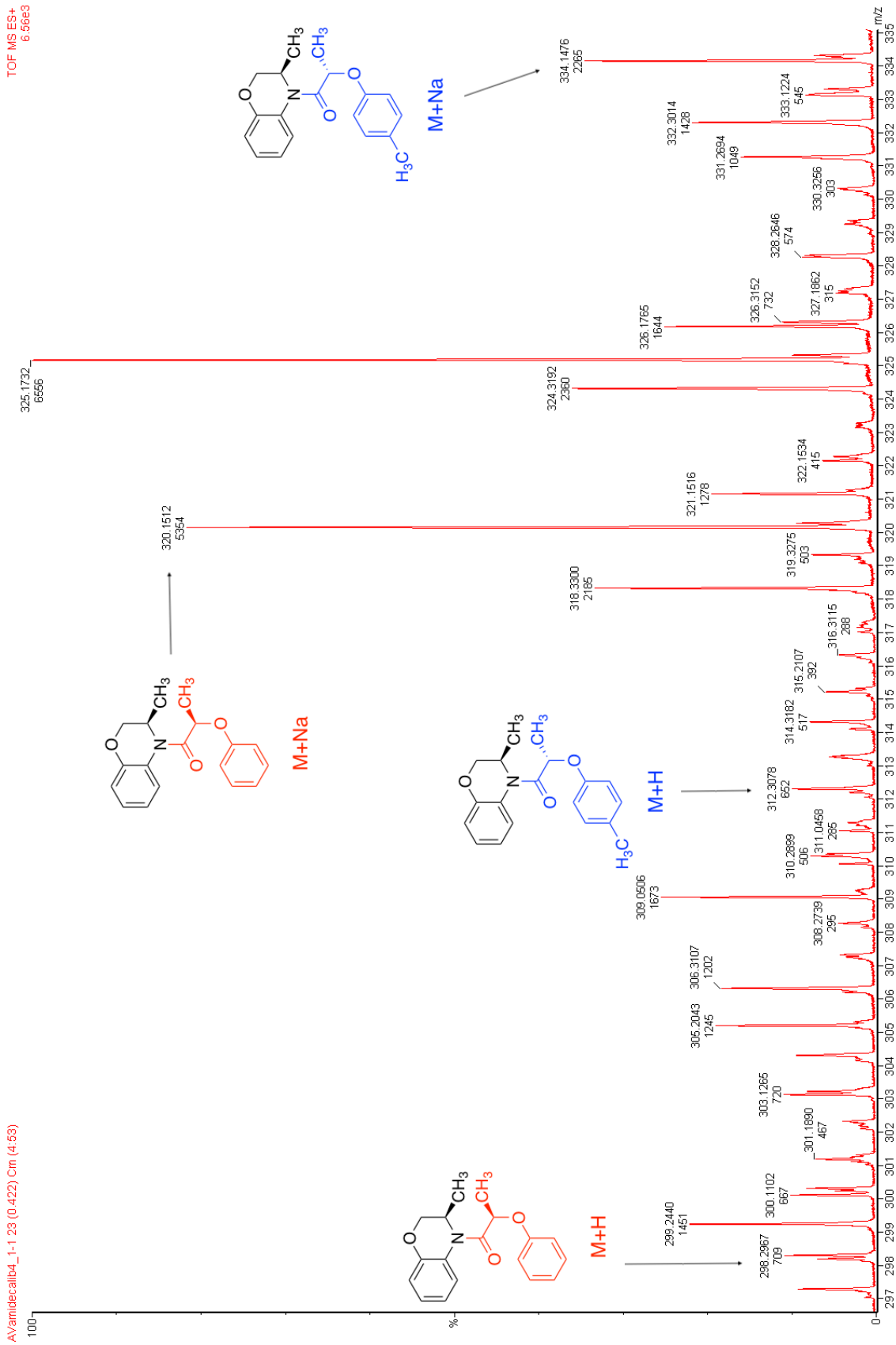

AVamidecalib1_10-1 21 (0.385) Cm (4:45)
TOF MS ES+
9.19e3
M+H
M+Na
M+H
M+Na
M+Na
m/z
%

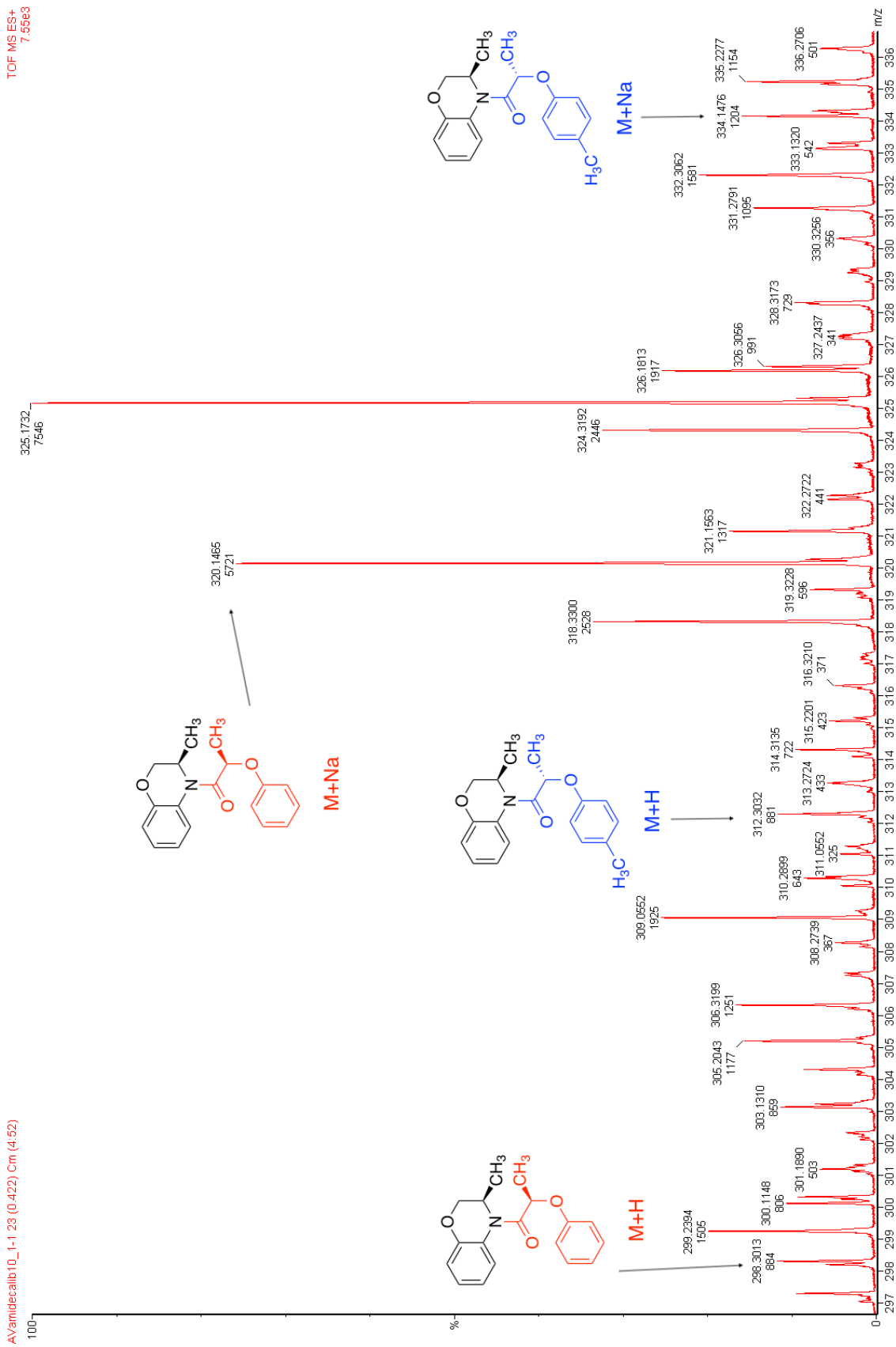

TOF MS ES+
1.03e4
AVamidecalib1_4-1 21 (0.385) Cm (3:42)
100
%
0
m/z
334.1524
10251
325.1780
6934
324.3239
2544
326.1813
1745
326.3152
660
328.3173
507
331.2791
1009
332.3110
1632
333.1562
501
320.1559
2028
320.2839
861
321.1658
478
318.3300
1259
317.2398
322
315.2201
459
314.3182
435
312.2003
835
310.2852
426
309.0552
1607
307.2335
462
306.3199
1196
305.2043
1131
304.3123
717
303.1310
671
301.1844
410
300.1148
639
299.2486
1428
M+Na
M+Na
M+H
M+H
H3C
H3C
CH3
CH3
CH3
CH3
N
O
O
O


AVamidecalib1_2-1 22 (0.404) Cm (4:48)
TOF MS ES+
1.03e4
100
%
0
m/z
M+H
M+Na
M+H
M+Na
334.1524
10318
335.1550
2874
325.1780
7973
320.1559
3629
309.0552
1926
299.2440
1406
298.3013
491


TOF MS ES+
2.18e4
AVamidecalib1_1-1 23 (0.422) Cm (2:55)
100
%
0
m/z
298 299 300 301 302 303 304 305 306 307 308 309 310 311 312 313 314 315 316 317 318 319 320 321 322 323 324 325 326 327 328 329 330 331 332 333 334 335 336 337 338
301.1890 681
304.3030 3149
305.1950 1603
312.1909 1179
315.2201 1628
317.2634 3045
318.2734 863
320.1418 16594
321.1516 4572
322.1582 718
325.1780 3340
331.1779 838
334.1379 21811
335.1501 6941
336.1590 1224
337.1111 4531
338.1180 1078
M+H
M+H
M+Na
M+Na


TOF MS ES+
6.00e3
AV_amidecalib2_1-1 22 (0.404) Cm (2:55)
100
%
0
m/z
M+Na
M+H
M+H
M+Na
325.1780
5999
324.3239
2287
326.1861
1510
326.3104
637
327.2437
289
328.2693
507
330.3304
260
331.2742
932
332.3014
1352
333.1320
480
334.1572
3082
335.2325
917
320.1512
3917
321.1563
888
322.1582
376
318.3300
2013
319.3275
469
317.2398
807
315.2201
422
314.3182
438
312.3032
563
309.0552
1477
310.2899
453
311.0505
253
307.2335
1291
308.2924
537
305.1996
1140
303.1265
654
303.2233
483
301.1936
424
299.2394
1395
300.1194
577
298.3013
602


TOF MS ES+
6.56e3
AVamidecalib4_1-1 23 (0.422) Cm (4:53)
100
%
0
m/z
M+H
M+Na
M+H
M+Na
299.2440
1451
298.2967
709
300.1102
667
301.1890
467
303.1265
720
305.2043
1245
306.3107
1202
308.2739
295
309.0506
1673
310.2699
506
311.0458
285
312.3078
652
314.3182
517
315.2107
392
316.3115
288
318.3300
2185
319.3275
503
320.1512
5354
321.1516
1278
322.1534
415
324.3192
2360
325.1732
6556
326.1765
1644
326.3152
732
327.1862
315
328.2646
574
330.3256
303
331.2694
1049
332.3014
1428
333.1224
545
334.1476
2265


TOF MS ES+
7.55e3
AVamidecalib10_1-1 23 (0.422) Cm (4:52)
100
%
0
m/z
325.1732
7546
324.3192
2446
326.1813
1917
326.3056
991
328.3173
729
327.2437
341
330.3256
366
331.2791
1095
332.3062
1581
333.1320
542
334.1476
1204
335.2277
1154
336.2706
501
320.1465
5721
321.1563
1317
322.2722
441
318.3300
2528
319.3228
596
316.3210
371
314.3135
722
315.2201
423
312.3032
861
313.2724
433
309.0552
1925
310.2899
643
311.0552
325
308.2739
367
305.2043
1177
306.3199
1251
303.1310
869
299.2394
1505
300.1148
806
301.1890
503
298.3013
884
M+Na
M+H
M+Na
M+H
H_3C
H_3C
CH_3
CH_3
O
N
O
O